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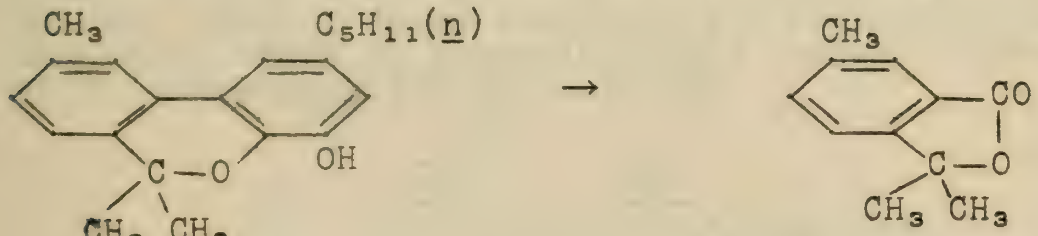
CANNABINOL AND CANNABIDIOL FROM MINNESOTA WILD HEMP

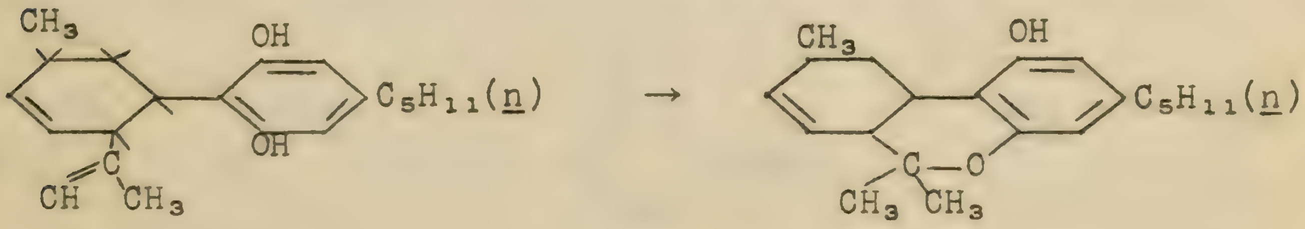
When the tops of the female plants of Cannabis sativa (hemp) are cut during the flowering period and extracted, there is obtained from the extract by distillation a viscous oil known as "red oil" from its color. This oil contains the physiologically active principle. Wood, Spivey and Easterfield in 1896 acetylated the red oil and obtained a crystalline substance which after purification was hydrolyzed to the substance they called cannabinol ($C_{21}H_{26}O_2$). Preliminary experiments were carried out on its constitution but the effective results were obtained by Cahn (1932-1936) who was the only investigator of a number able to repeat the isolation of cannabinol. He reported it to have the formula I,



I II

after a study of its nitration product. It was possible to oxidize this latter to a substance which upon replacement of the nitro group by hydrogen gave compound II identified by synthesis. Oxidation of I to n-caproic acid, the presence of an hydroxyl and the easy introduction of two nitro groups into the right-hand ring led Cahn to postulate structure I with doubt obviously in regard to the positions of the n-amyl and hydroxyl groups. Cannabinol is physiologically inactive.

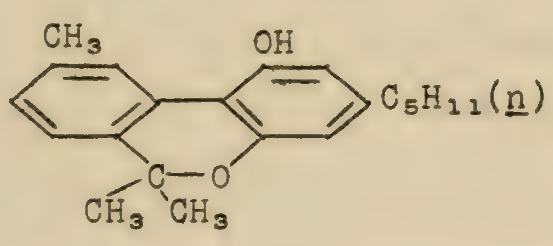
From Minnesota wild hemp red oil, no cannabinol could be isolated by the methods previously described. Through a study of various hydroxyl reagents with the red oil it was found possible to isolate a crystalline bis-3,5-dinitrobenzoate of a compound containing four more hydrogens than cannabinol ($C_{21}H_{30}O_2$). This substance was called cannabidiol and is physiologically inactive. Its structure is postulated as III on the basis of the following facts.



III IV

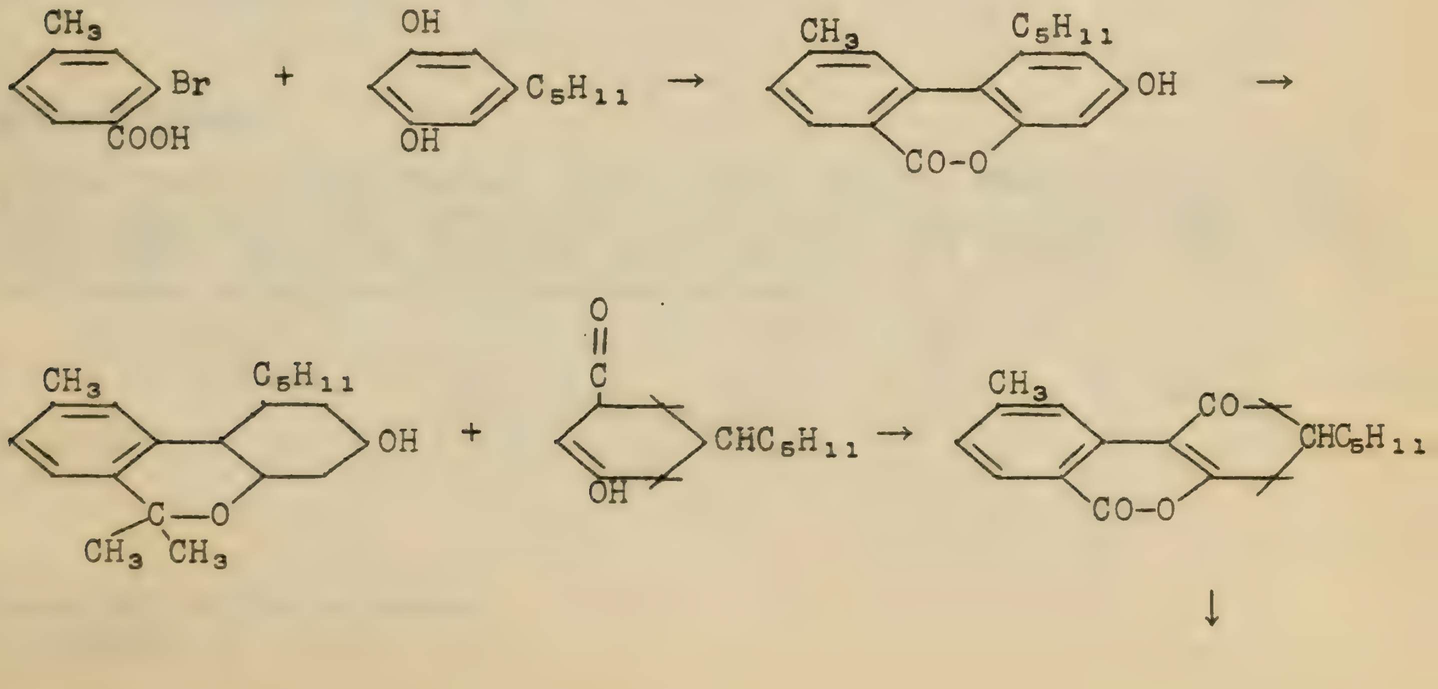
(1) Presence of two hydroxyl groups, (2) presence of two double bonds by catalytic hydrogenation, (3) oxidation to *n*-caproic acid, (4) cleavage by pyridine hydrochloride to *p*-cymene and olivetol (1,3-dihydroxy-5-*n*-amyl benzene), (4) oxidation of the tetrahydrocannabidiol to menthane carboxylic acid identified by synthesis, (5) comparison of the absorption spectra with analogous synthetic compounds with the linkage between the hydroxyls and between one hydroxyl and the alkyl group, (6) oxidation with ozone to formaldehyde, (7) isomerization to tetrahydrocannabinol, (8) shifting of the double bond in tetrahydrocannabinol without forming a conjugation with the benzene ring.

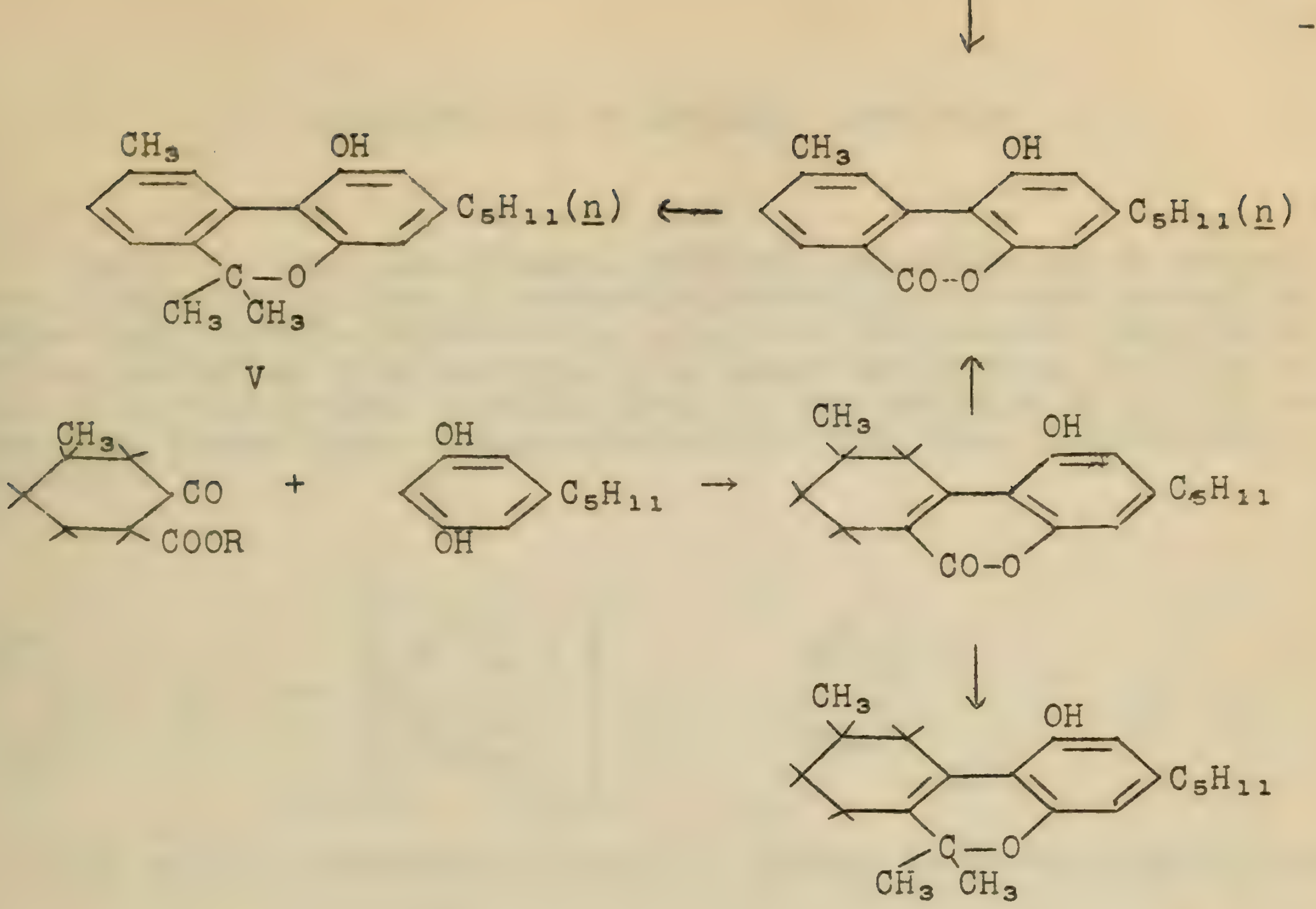
The tetrahydrocannabinol (IV) proved to be very active physiologically and the corresponding compound, presumably with the double bond shifted toward the methyl substituted carbon, is also active. Both of these compounds are reduced to the same hexahydrocannabinol which is physiologically active. Upon dehydrogenation of IV, cannabinol (V) was obtained.



V

With the cleavage of cannabidiol to 1,3-dihydroxy-5-*n*-amyl benzene, the probability of the same residue in cannabinol and the incorrectness of Cahn's formula were established. This was confirmed by two independent syntheses of cannabinol shown below.





V

VI

Compound VI is of peculiar interest because it is a tetrahydrocannabinol with the double bond conjugated to the benzene ring. It is, of course, optically inactive but proved to be physiologically active. The dihydro reduction product of VI was also active.

Cannabinol was also isolated from Minnesota wild hemp red oil by removing the cannabidiol and precipitating the cannabinol as the 3,5-dinitrophenyl urethan.

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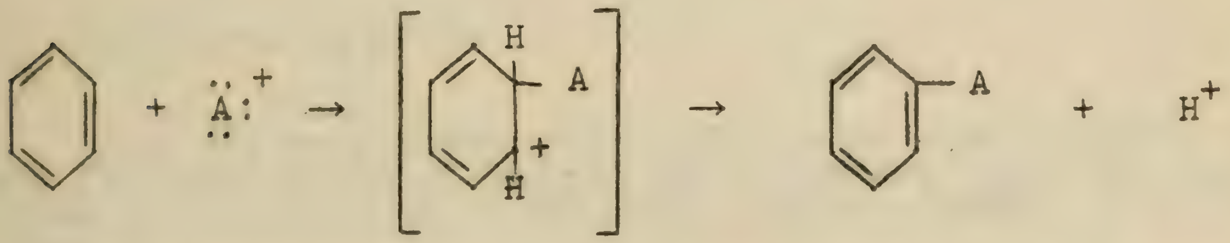
Adams, Hunt, Clark, Baker, Pease, Cain, Wolff, Wearn, J. Am. Chem. Soc., 62, 196, 732, 735, 1770, 2194, 2197, 2201, 2204, 2208, 2215, 2245, 2401, 2402, 2405, 2566; Science, 92, 115 (1940). Other recent references are given in these articles.

Reported by Roger Adams
September 18, 1940

SUBSTITUTION IN AROMATIC COMPOUNDS

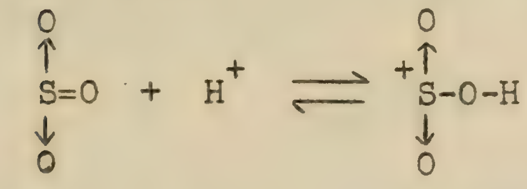
There has been considerable evidence accumulating in recent years that substitution in aromatic compounds proceeds through an active intermediate deficient in a pair of electrons. This intermediate satisfies this deficiency by associating with the labile pair of electrons from a double bond in the aromatic ring, the complex thus formed then losing a proton to yield the substitution product.



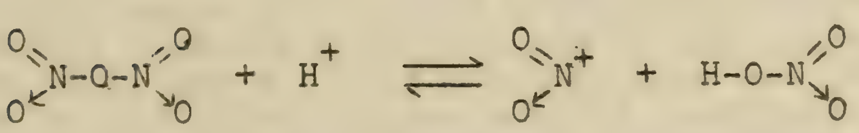
The active intermediate A may be formed by the following means.

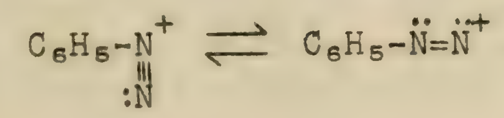
$$\mathrm{Cl_2 + FeCl_3} \rightleftharpoons \mathrm{:\underset{\cdot\cdot}{\ddot{Cl}}}^{+}\ \mathrm{(FeCl_4)^-}$$

$$\mathrm{RX + AlX_3} \rightleftharpoons \mathrm{:\underset{\cdot\cdot}{\ddot{R}}}^{+}\ \mathrm{(AlCl_4)^-}$$



$$\begin{array}{c}\mathrm{O}\\ \uparrow\\ \mathrm{S{=}O}\\ \downarrow\\ \mathrm{O}\end{array} + \mathrm{H}^+ \rightleftharpoons \begin{array}{c}\mathrm{O}\\ {}^{+}\uparrow\\ \mathrm{S{-}O{-}H}\\ \downarrow\\ \mathrm{O}\end{array}$$





$$\mathrm{C_6H_5{-}}\begin{array}{c}\mathrm{N}^+\\ \equiv\\ \mathrm{:N}\end{array} \rightleftharpoons \mathrm{C_6H_5{-}\ddot{N}{=}\ddot{N}}^+$$

On the basis of this mechanism, orientation will be effected simply by a shift of the extra, labile pair of electrons in the double bond toward the o- and p-positions or toward the m-positions. Such a shift could be induced by the electrostatic effect of a substituent group, which in most simple cases, would be governed chiefly by the atom directly attached to the double bond.

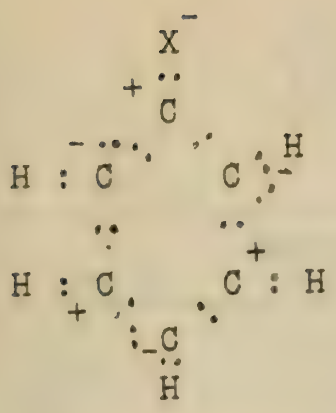
[illegible]

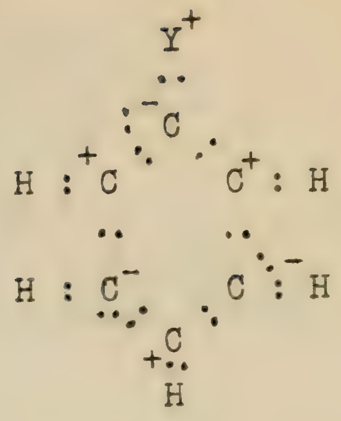
[illegible] substitution in aromatic compounds [illegible] intermediate [illegible]

[illegible] A may be formed in the following ways:

[illegible]

[illegible]





o,p-directing group

Actually many modern orientation rules such as those of Hammick and Illingworth and of Latimer and Porter are empirical approximations of the polarity of the atom directly attached to the aromatic ring.

To determine accurately whether the electrostatic effect of substituent groups governs their orienting influence, the actual charge on each atom of the substituent group, as well as its position relative to the labile electrons of the double bond, must be taken into account. This has been done for a large number of groups of known orienting influence. The effect of each atom in the group was calculated as

$$\frac{q}{d^2}\cos\theta$$

where q is the charge on the atom (calculated from dipole moment data), d is the distance from the atom to the center of adjacent bond in the ring, and θ is the angle between the line d and the bond. When an atom could assume various positions with regard to the electrons, the arithmetic mean of the extremes was used. The results for the various atoms in the group were then added algebraically. The results of these calculations are summarized in the table along with the experimentally determined orienting influence.

The Relative Polarizing Influence of Various Substituent Groups on an Adjacent Double Bond Compared with Their Orienting Influence

Group	Charge on α-Atom	Polarizing Force on Electrons	% *meta*-Orientation[a]
NH_2	-0.56	-6.3	-
OH	-0.44	-6.2	3
F	-0.23	-4.9	-
Cl	-0.20	-3.0	-
$C(CH_3)_3$	0	-2.7	-
Br	-0.19	-2.4	-
I	-0.16	-1.7	-
CH_3	-0.18	-1.7	4
CH_2Cl	+0.08	+1.6	4
CH_2Br	0.07	1.6	7
CH_2F	.11	1.7	17
H	0.06	2.0	(40)
CH_2NO_2	-0.06	3.0	50
$CHCl_2$	+0.22	3.3	34
$CH_2NH_3^+$	-0.06	3.9	49
$C\begin{smallmatrix}{/\!/}O\\ -R\end{smallmatrix}$	+0.40	3.9	55
SO_3H	0.54	4.0	72
CCl_3	.30	4.1	64
$CONH_2$	.46	4.1	69
$C\begin{smallmatrix}{/\!/}O\\ -H\end{smallmatrix}$	.34	4.3	79
$CH_2N(CH_3)_3^+$	-0.06	4.7	88
$C(COOCH_3)_3$	0	4.8	57
$COOH$	0.53	5.5	82
$COCl$	.60	7.6	90
$C{\equiv}N$	.66	7.9	80
NO_2	.79	9.7	93
NH_3^+	.19	10.8	100
$N(CH_3)_3^+$	.76	14.6	100

(a) L. F. Fieser, Gilman, "Organic Chemistry, Vol. I, p. 140.

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Reported by C. C. Price
September 25, 1940

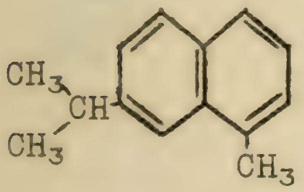
THE STRUCTURE OF EREMOPHILONE AND RELATED SESQUITERPENE KETONES

J. L. Simonsen -- University College of North Wales

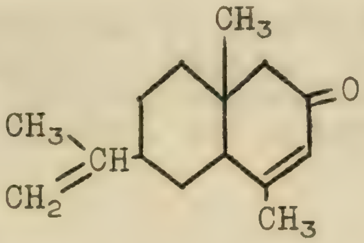
In 1932 Bradfield, Penfold and Simonsen reported the isolation of three optically active sesquiterpene ketones from the wood oil of Eremophila Mitchelli:

Eremophilone -- $C_{15}H_{22}O$; m.p. 41-2°; $[\alpha]_{5461}$ -207°
Hydroxyeremophilone -- $C_{15}H_{22}O_2$; m.p. 66-7°; $[\alpha]_{5461}$ +153°
Hydroxydihydroeremophilone -- $C_{15}H_{24}O_2$; m.p. 102-3°; $[\alpha]$ +94°

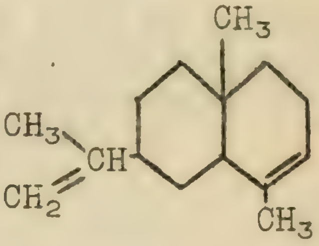
By dehydrogenation, they were shown to be related to eudalene (I), and were the first bicyclic sesquiterpene ketones to be isolated. The structures that Simonsen has finally assigned to these compounds (IV, XII, XVI) are significant because they are the first terpenes to be shown not to obey the isoprene rule. The formulas first suggested in 1932 (only the one for eremophilone is shown, formula II) were closely related to the known sesquiterpene, α-selinene (III) and obeyed the isoprene rule. However, the evidence outlined below clearly indicates that they were incorrect. (All rings are saturated except where double bonds are shown.)



Eudalene (I)

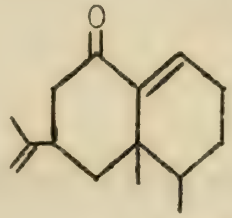


1932 Formula (II)



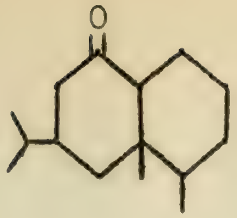
α-Selinene (III)

A. Eremophilone:

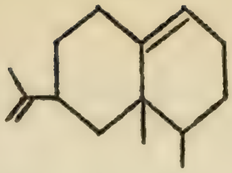


(IV)

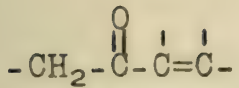
Group Indicated	Evidence
$-\overset{\mid}{C}=O$	a. Soluble in $NaHSO_3$, ketone regenerated by alkali. b. Forms semicarbazone, ketone regenerated with oxalic acid.
$2\ -\overset{\mid}{C}=\overset{\mid}{C}-$ unconjugated	a. Absorbs 2 mols of H_2 with Pd-C catalyst to form tetrahydroeremophilone (V). b. Wolff-Kishner reduction of eremophilone gives a hydrocarbon (VI) which shows 2 double bonds when titrated with monoperphthalic acid, and is also not reduced by Na in EtOH. Both these reactions indicate that the double bonds are not conjugated.



(V)

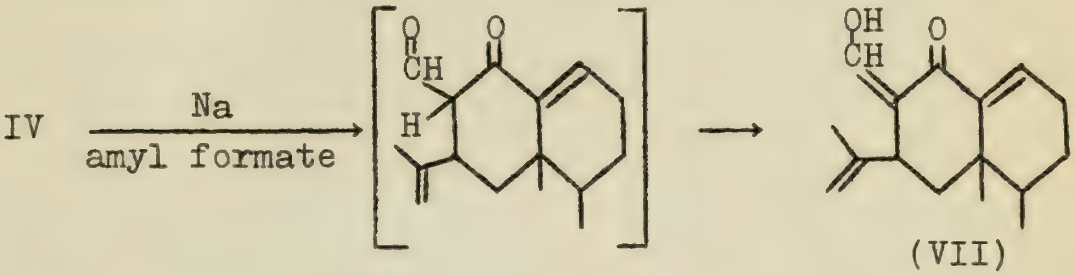


(VI)



$-CH_2-\overset{O}{\overset{\|}{C}}-\overset{|}{C}=\overset{|}{C}-$

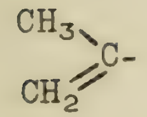
a. Eremophilone forms a crystalline hydroxymethylene derivative (VII) with sodium and amyl formate:



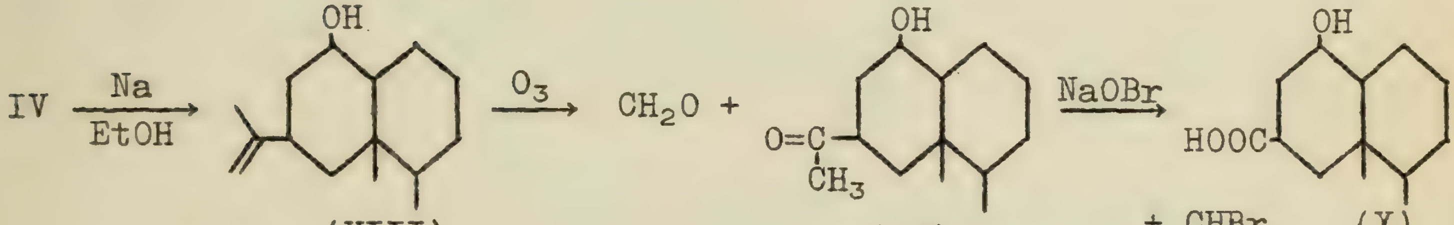
(VII)

b. Eremophilone forms an oxide with alkaline H_2O_2. Weitz and Scheffer have shown this to be characteristic of α,β-unsaturated ketones only. Catalytic hydrogenation of the oxide shows 1 double bond.

c. Absorption spectrum is very similar to that of mesityl oxide and cholestenone, both α,β-unsaturated ketones.

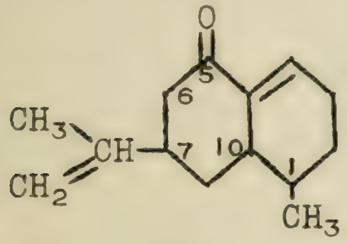


a. Eremophilone is reduced by Na in EtOH to dihydroeremophilol (VIII). Ozonization of VIII gives CH_2O and a hydroxy-ketone (IX) which reacts with NaOBr to give $CHBr_3$ and a hydroxy-acid (X).



(VIII) (IX) (X)

These groups were all placed (XI) according to the following evidence:



(XI)

a. Dihydroeremophilol (VIII) is dehydrogenated to eudalene (I). This fixes one methyl and the isopropyl group.

b. The hydroxymethylene derivative (VII), after reduction, is dehydrogenated to 1,6-dimethyl-7-isopropylnaphthalene. This fixes the methylene group as carbon 6, and indicates that the keto group must be on carbon 5, as proved by the following:

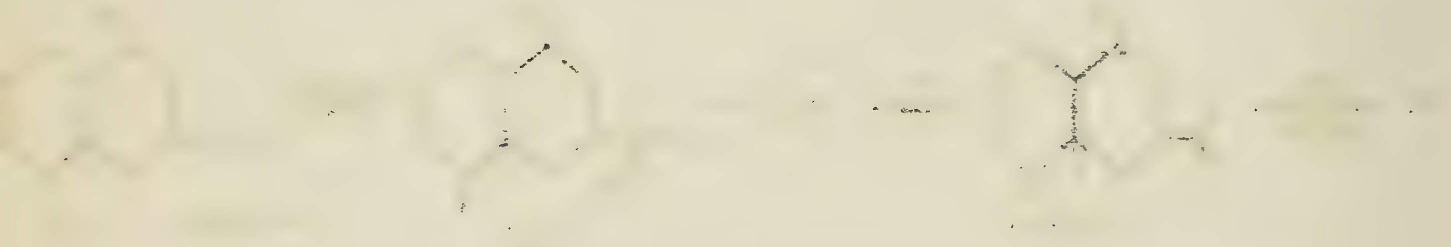
c. When tetrahydroeremophilone (V) is treated with CH_3MgI and the product dehydrogenated, 1,5-dimethyl-7-isopropylnaphthalene is formed.

Finally, the angular methyl group is placed at carbon 10 by the

[illegible]

[illegible]

[illegible]



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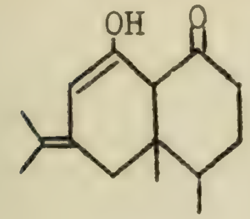
[illegible]

[illegible]

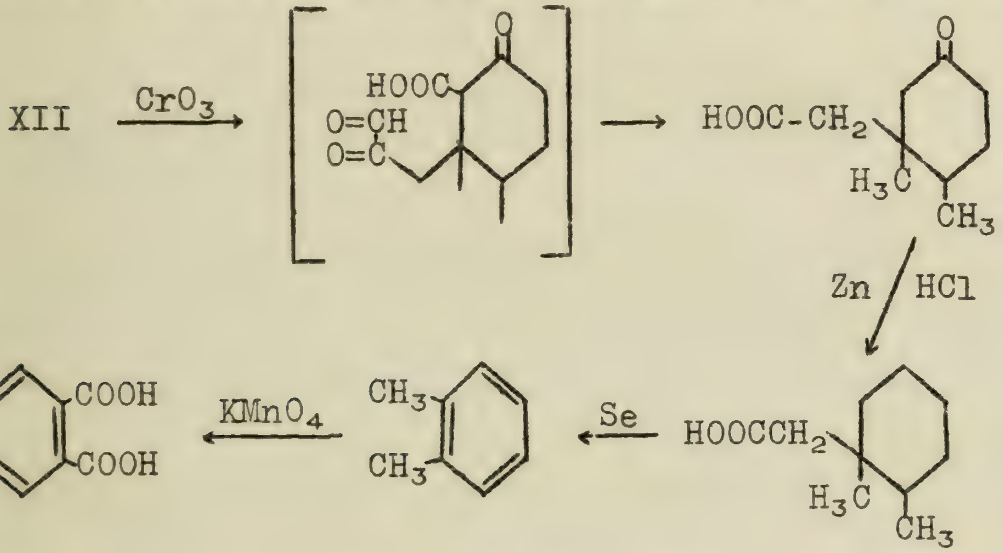
conversion of eremophilone oxide to hydroxyeremophilone (XII) in which the position of the angular methyl is proved by degradation experiments, as described below.

B. Hydroxyeremophilone: Although hydroxyeremophilone (XII) is soluble in aqueous $NaHSO_3$, no ketone derivatives could be obtained from it or from its benzoate or acetate. Moreover, the benzoate does not react with CH_3MgI. The appearance of an intense bluish-black color with $FeCl_3$ indicates the presence of an enolic hydroxyl. The conversion of eremophilone oxide to hydroxyeremophilone, already mentioned above, proves that the eudalene skeleton (I) is present in hydroxyeremophilone; but ozonization of the benzoate of XII gives acetone, showing the side chain to be $(CH_3)_2C=C$.



(XII)

The degradation experiments which locate the positions of the enolic hydroxyl and the angular methyl are formulated as follows:

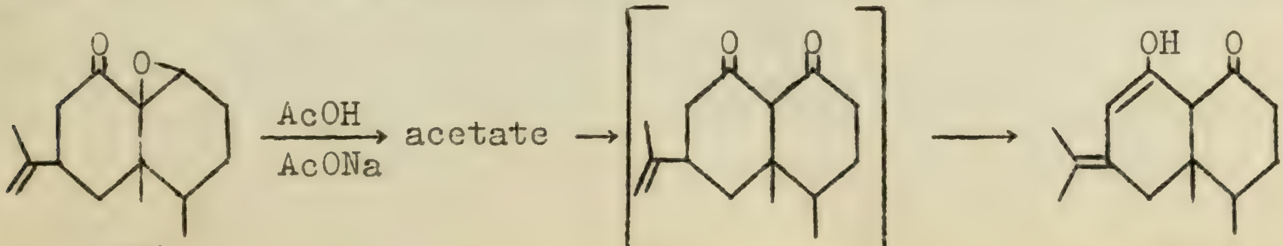


(XIII)

The structure of this acid was proved by synthesis.

d-1,2-Dimethylcyclohexyl-acetic Acid (XIV)

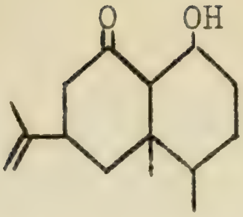
The keto-acid (XIII) is also obtained by ozonization of the benzoate or the methyl ether of hydroxyeremophilone. The keto group is placed in position 4 because of the formation of hydroxyeremophilone (XII) from eremophilone oxide (XV), a reaction which has already been mentioned twice. Baker and Robinson have shown that keto-ethylene oxides of this type (XV) go to 1,2-diketones with AcOH-AcONa. Since a 1,2-diketone is impossible with XV, Simonsen considers that the product (i.e. hydroxyeremophilone) is a 1,3-diketone which enolizes:



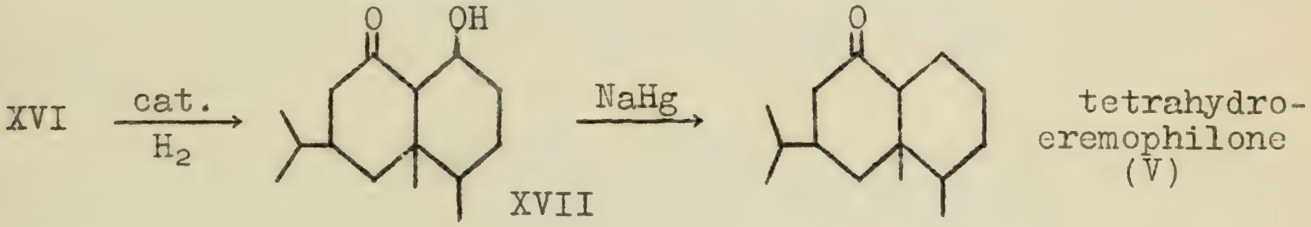
(XV)

(XII)

C. Hydroxydihydroeremophilone:


(XVI)

This compound gives no color with $FeCl_3$. It forms a dinitrophenylhydrazone and a dinitrobenzoate, and catalytic hydrogenation shows the presence of 1 double bond. The keto group is easily enolized, since with Ac_2O a diacetate is formed, and the position of the keto group is fixed by the following reactions:



Ozonization of XVI gives CH_2O, indicating an isopropenyl side chain, and the hydroxyl group is placed in position 4 by analogy to hydroxyeremophilone (XII).

Anomalous Reaction: Hydroxyeremophilone (XII) and hydroxydihydroeremophilone (XVI) are reduced by Na in EtOH to glycols which are oxidized by $PbAc_4$ to the same dibasic acid, $C_{15}H_{26}O_4$. Lead tetraacetate has always been considered a specific reagent for 1,2-glycols, yet in this case the glycols oxidized must be 1,3. Although it is well-known that groups in the peri position in the naphthalene nucleus show behavior similar to that of o-substituents, the 1,8-dihydroxydecalins have not been sufficiently studied to verify this oxidation. Simonsen has indicated that he intends to investigate this point.

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Reported by E. H. Riddle
September 25, 1940

THE DETERMINATION OF THE STRUCTURE OF PANTOTHENIC ACID

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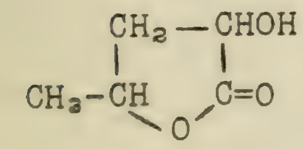
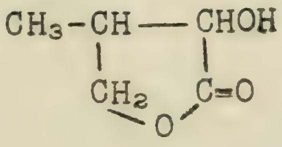
Pantothenic acid, a member of the vitamin B group, occurs in a great variety of foods. It has growth-promoting properties and a curative action against dermatitis developing in chicks fed a heated diet.

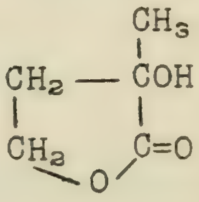
Analysis of calcium pantothenate obtained from aqueous liver extract by solution in alcohol, adsorption on charcoal and elution with aqueous ammonia, fractionation of alkaloidal salts and finally fractionation of the calcium salt, indicated the acid to have the formula $C_8H_{15}O_5N$. It has been shown later that the sample was of only about 90 per cent purity. Because of its extremely high solubility in water and the low volatility of its derivatives, analytically pure pantothenic acid has not yet been separated from a natural source.

Hydrolysis of pantothenic acid gave β-alanine, $H_2NCH_2CH_2CO_2H$. The other fragment was an acid which readily lactonized. This acid gave positive tests (color with $FeCl_3$, evolution of CO with hot sulfuric acid) for an α-hydroxyl group. The activity of pantothenic acid was destroyed by treatment with acetaldehyde, benzaldehyde or acetone, indicating the formation of a cyclic acetal. This, together with the ease of lactonization, pointed to a second hydroxyl on the γ-carbon atom.

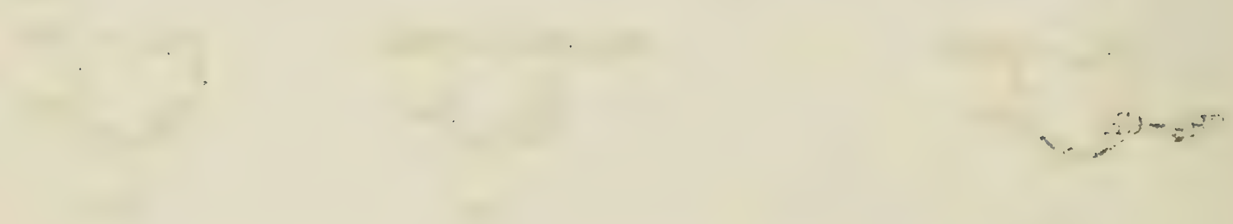
Accordingly, the lactones of the three possible α,γ-dihydroxyvaleric acids (I, II, III) were synthesized and combined with β-alanine. The products had very slight biological activity.

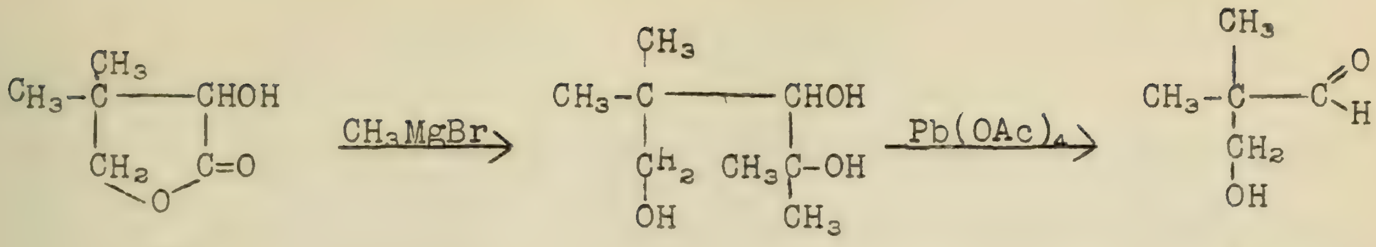

I


II


III

It was then discovered that the crucial lactone could be obtained as a pure levo-rotatory solid from concentrates containing as little as 3 per cent of pantothenic acid. Analysis showed it to have six carbons, the formula being $C_6H_{10}O_3$. It was shown to have the structure (IV) by the following degradation.

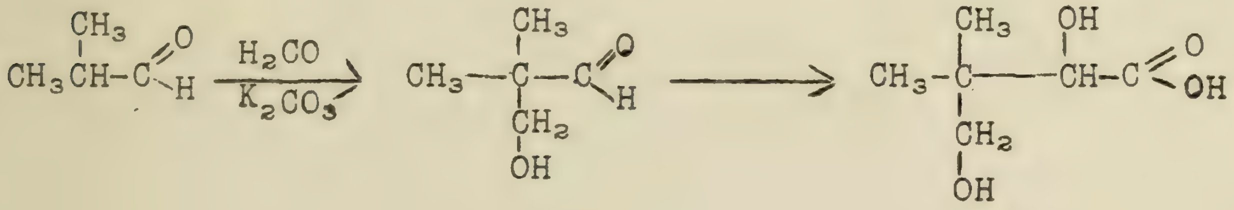




IV V

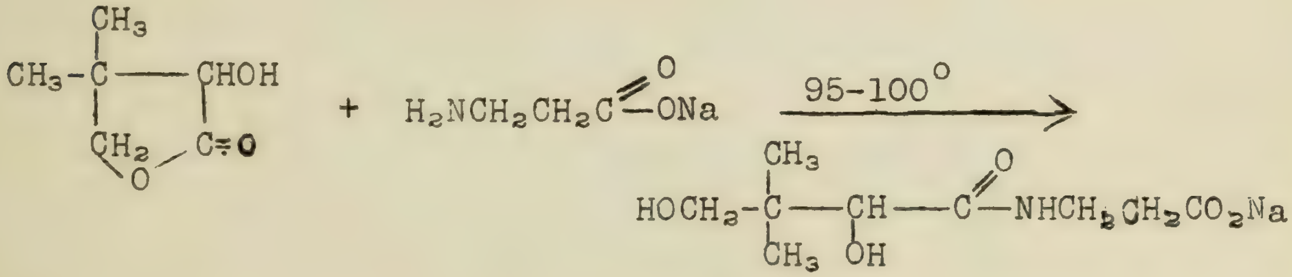
The aldehyde (V) was identified by oxidation to β-hydroxy-α,α-dimethylpropionic acid and comparison of the latter with an authentic sample.

In the synthesis of pantothenic acid the dihydroxy acid (VI) was prepared by a cyanohydrin synthesis on the aldehyde (V).



V VI

This acid (VI) was resolved by the method of Pope and Gibson, in which one mole of alkaloid is allowed to come to equilibrium with two moles of the alkali salt of the racemic acid. In the present case, this procedure gave directly the nearly pure quinine salt of the dihydroxy acid corresponding to the levo-rotatory lactone. The lactone was obtained by continuous ether extraction of a solution of the salt in aqueous acid. The sodium salt of pantothenic acid is best obtained by heating the lactone with β-alanine sodium salt in the absence of a solvent.



Sodium Pantothenate

Pantothenic acid obtained from the levo-rotatory lactone is dextro-rotatory. The enantiomorph is without biological activity.

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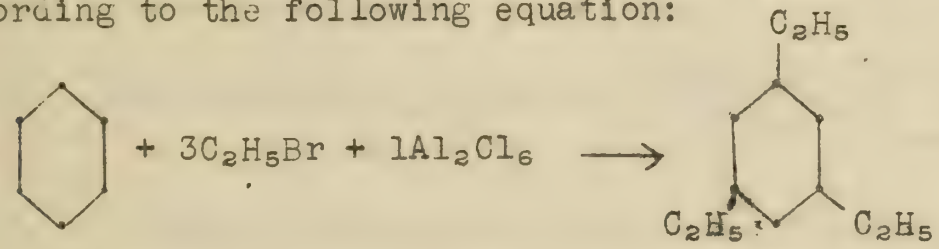
Reported by H. R. Snyder
October 2, 1940

SOME RECENT DEVELOPMENTS IN THE FRIEDEL-CRAFTS REACTION

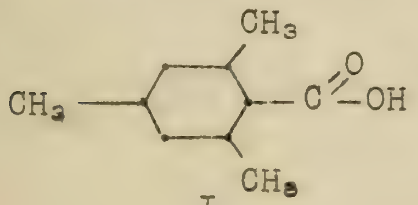
Norris - Massachusetts Institute of Technology

For the past five years, until his death in August, Professor Norris was interested in various aspects of the Friedel-Crafts reaction. From work on the rearrangement of aromatic hydrocarbons in the presence of aluminum chloride, he developed a method for preparing symmetrical trialkyl benzenes according to the following equation:

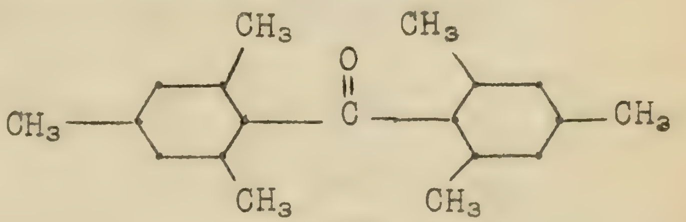
1 

85-90 per cent

It was found that these trialkyl benzenes form stable complexes with aluminum halides and hydrogen halides, so stable in fact that they can be held at a pressure of 0.015 to 0.030 mm. for eight hours without decomposition. The ones studied most extensively were $Al_2Br_6 \cdot \underline{s}-C_6H_3(C_2H_5)_3 \cdot HBr$ and $Al_2Br_6 \cdot \underline{s}-C_6H_3(CH_3)_3 \cdot HBr$. When treated with carbon dioxide the mesitylene complex yielded 27 per cent of mesitoic acid (I) and 45 per cent of dimesityl ketone (II).



I



II

The triethylbenzene complex proved more inert, only traces of the acid and ketone being produced.

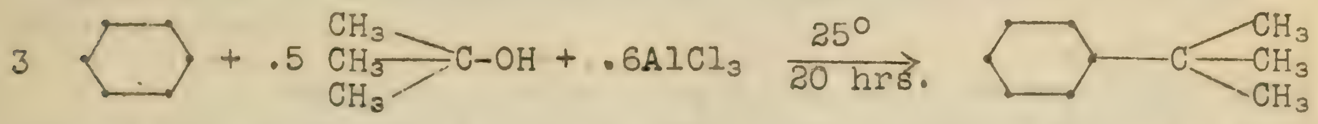
These complexes were investigated as possible intermediates in the Friedel-Crafts reaction. When treated with acetyl chloride, the triethylbenzene complex yielded triethylacetophenone in 67 per cent yield. Of interest in this connection was the fact that in the acetylation of benzene with acetyl bromide and aluminum chloride 77 per cent of the hydrogen halide given off was hydrogen chloride. Analogously 92 per cent of the chlorine in the $AlCl_3 \cdot 2C_6H_5NO_2$ complex could be replaced with bromine by treatment with HBr.

Alcohols reacted with aluminum chloride according to the following equations:

$$C_2H_5OH + AlCl_3 \longrightarrow C_2H_5OH \cdot AlCl_3 \xrightarrow{95^o} HCl + C_2H_5OAlCl_2$$

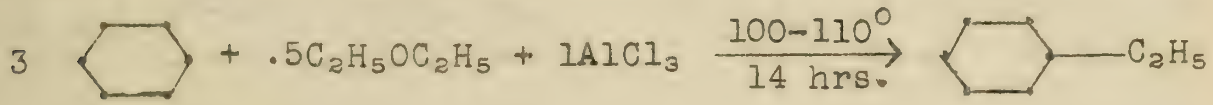
$$C_2H_5OAlCl_2 \xrightarrow{150^o} \underset{98 \text{ per cent}}{C_2H_5Cl + AlOCl}$$

By using more than the one mole of aluminum chloride necessary for the above reaction to take place it was possible to employ alcohols in the Friedel-Crafts reaction.



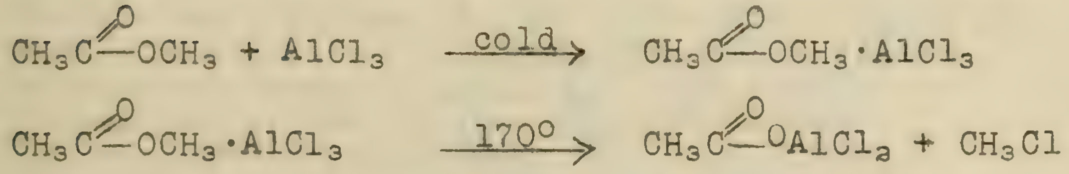
84 per cent

Ethers behaved similarly:



36 per cent

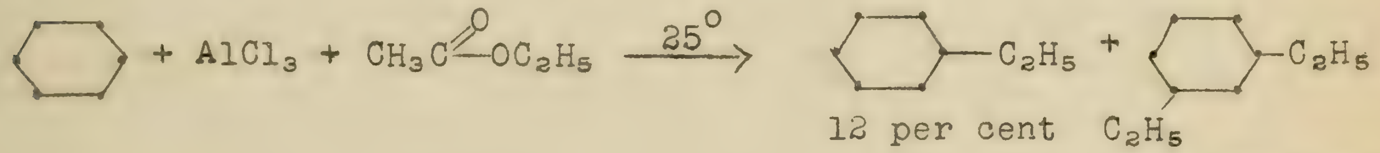
Esters reacted with aluminum chloride as follows:



$$\mathrm{CH_3\overset{O}{C}{-}OCH_3 + AlCl_3 \xrightarrow{cold} CH_3\overset{O}{C}{-}OCH_3\cdot AlCl_3}$$

$$\mathrm{CH_3\overset{O}{C}{-}OCH_3\cdot AlCl_3 \xrightarrow{170^\circ} CH_3\overset{O}{C}{-}OAlCl_2 + CH_3Cl}$$

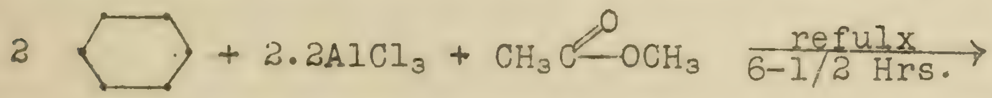
Alkylation with esters occurred at a much lower temperature than acylation, so that by controlling this factor it was possible to alkylate only, as in the following case:



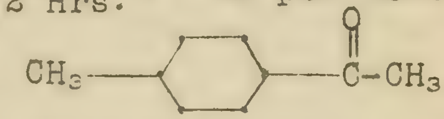
12 per cent

51 per cent

or alkylate and acylate at the same time as in the following:

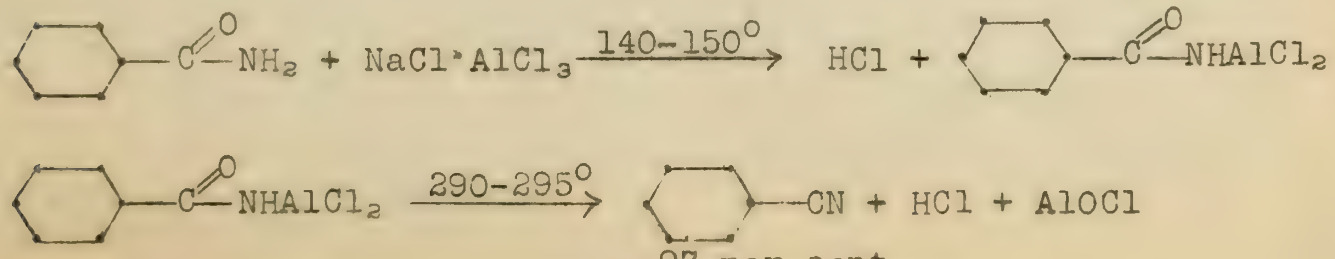


45 per cent of mixed ketones of which 83 per cent was



In all ester reactions a mixture of products was produced.

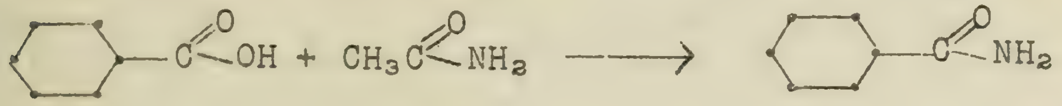
When an attempt was made to extend this reaction to amides, it was found that they were dehydrated by the aluminum chloride.



97 per cent

This was accordingly developed as a general method for preparing nitriles by which eleven were made in 29-97 per cent yield. The sodium chloride-aluminum chloride complex was used to moderate the reaction.

In connection with this amide work it was found that amides and acids exist in the same type of equilibrium as esters and acids and acid chlorides and acids.



53 per cent

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Reported by W. S. Emerson
October 2, 1940

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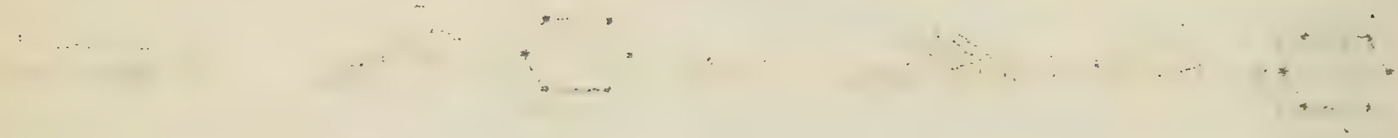

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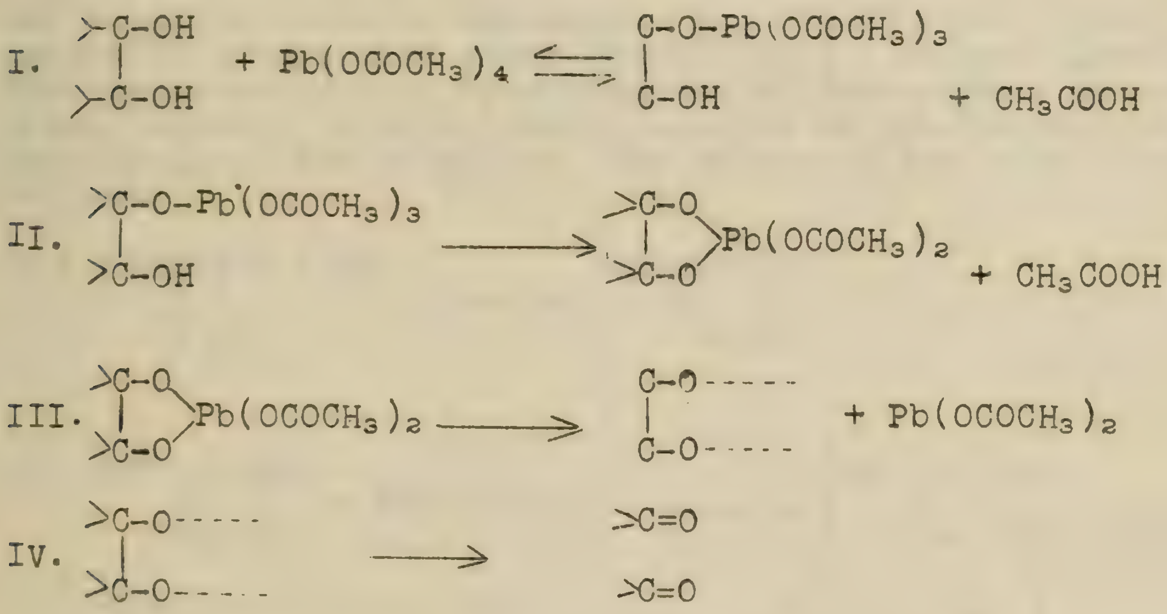
OXIDATIVE CLEAVAGE OF CARBON—CARBON BONDS

Criegee, Technische Hochschule, Karkruhe
Milas, Massachusetts Institute of Technology,
Cambridge, Massachusetts

I. Lead Tetraacetate

Previous to the year 1928 there was almost no general method available for the smooth cleavage of simple -C-C- bonds. In this year Malaprade discovered that α-glycols could be oxidized to aldehydes or ketones by means of periodic acid. Two years later, without knowledge of Malaprade's work, Criegee proposed the use of lead tetraacetate as the oxidizing agent for the cleavage of α-glycols. Since that time "Criegee's reagent" has played an important part in the oxidative cleavage of α-glycols and related compounds. Criegee has postulated the following mechanism for the glycol cleavage:



$$\text{I.}\quad \begin{array}{l}>\!C\!-\!OH\\ \;|\\ >\!C\!-\!OH\end{array} + Pb(OCOCH_3)_4 \rightleftharpoons \begin{array}{l}C\!-\!O\!-\!Pb(OCOCH_3)_3\\ |\\ C\!-\!OH\end{array} + CH_3COOH$$

$$\text{II.}\quad \begin{array}{l}>\!C\!-\!O\!-\!Pb(OCOCH_3)_3\\ \;|\\ >\!C\!-\!OH\end{array} \longrightarrow \begin{array}{l}>\!C\!-\!O\\ \;|\\ >\!C\!-\!O\end{array}\!\!>\!Pb(OCOCH_3)_2 + CH_3COOH$$

$$\text{III.}\quad \begin{array}{l}>\!C\!-\!O\\ \;|\\ >\!C\!-\!O\end{array}\!\!>\!Pb(OCOCH_3)_2 \longrightarrow \begin{array}{l}C\!-\!O\text{-----}\\ |\\ C\!-\!O\text{-----}\end{array} + Pb(OCOCH_3)_2$$

$$\text{IV.}\quad \begin{array}{l}>\!C\!-\!O\text{-----}\\ \;|\\ >\!C\!-\!O\text{-----}\end{array} \longrightarrow \begin{array}{l}>\!C\!=\!O\\ \\ >\!C\!=\!O\end{array}$$

Reaction I is an alcoholysis of the lead tetraacetate and is reversible. Reaction II likewise represents an alcoholysis with the splitting out of a second mole of acetic acid and with the formation of a cyclic lead acetate glycolate. This cyclic intermediary explains the fact that the cis-diol is always more rapidly oxidized than the isomeric trans-compound. The oxidation occurs in step III whereby the lead is reduced to the bivalent state and the original diacetate cleaves to form a 1,4-biradical with two "free valences" on the oxygen atoms. This unstable biradical then undergoes a molecular cleavage between carbon atoms to form the end products.

For the majority of organic reactions the use of lead tetraacetate as an oxidative cleaving agent shows three distinct

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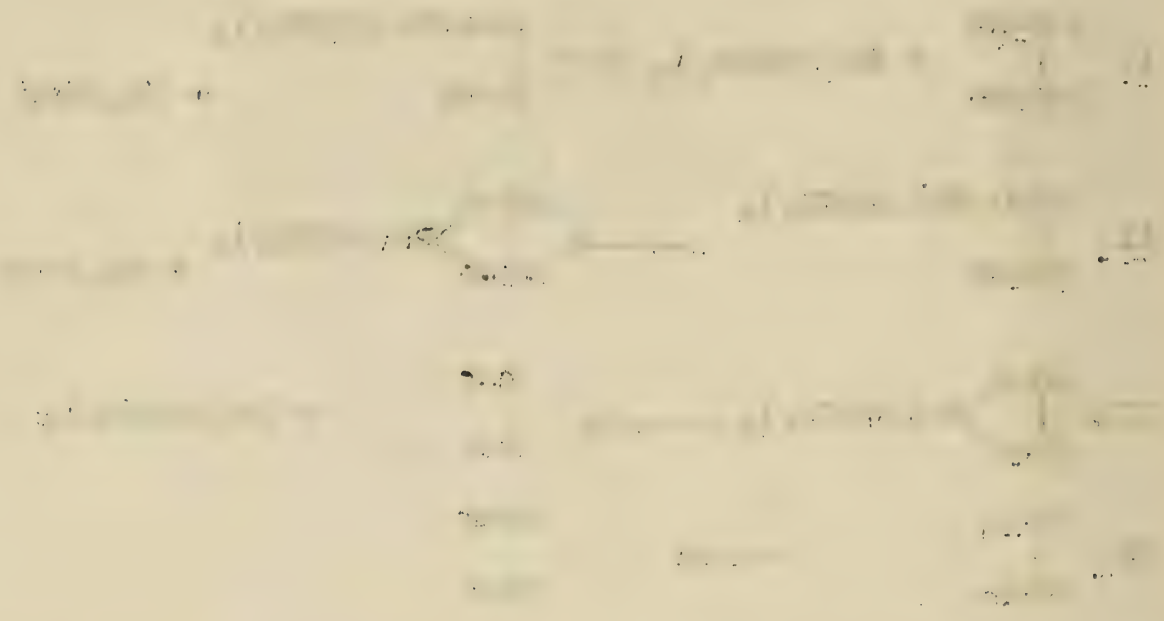

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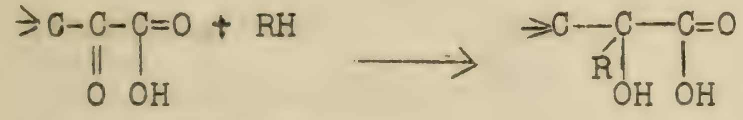
advantages; (1) it proceeds quantitatively, (2) it possesses a high specificity, showing no reaction toward primary alcohols, 1,3- or 1,4-diols, 1,2-diols with masked groups, or aldehydes or ketones, (3) the carbon-carbon bonds may be cleaved in dilute solution at room temperature. Lead tetraacetate was formerly thought to be effective as an oxidizing agent only in non-aqueous solvents. In 1939 Baer found, however, that the cleavage may be carried out in moist organic solvents and even in aqueous solution if the velocity of oxidation be higher than that of the hydrolysis of the oxidizing agent. From the oxidation of an aqueous solution of pinacol he obtained a 95 per cent yield of acetone.

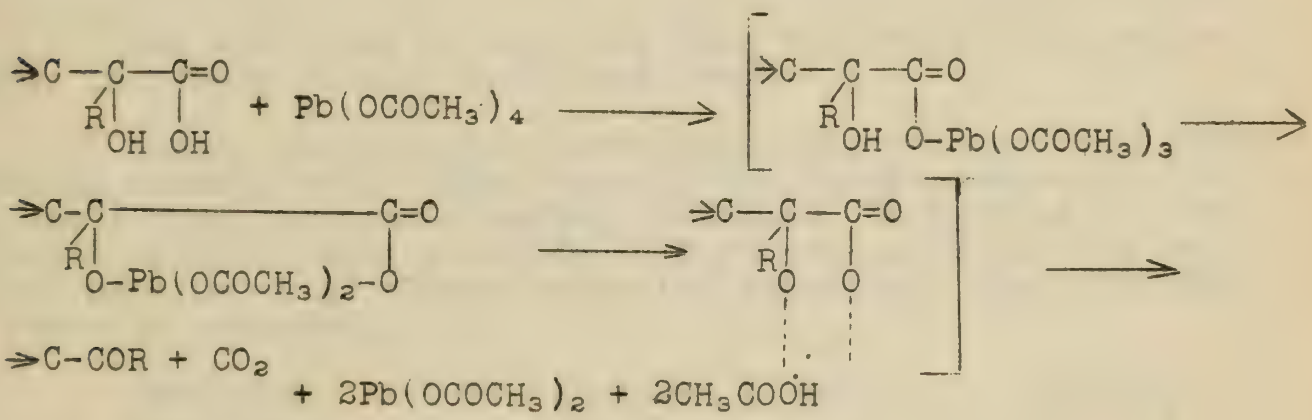
Recently the use of this reagent has been extended to naturally-occurring α-glycols, sugars, glycosides, and α-glycerides. Likewise replacing hydroxyl by amino groups has no effect on the reagent and consequently α-amino acids and α-diamines fall into this class of compounds. Within the past year Baer has shown that α-keto acids and α-keto alcohols, despite their apparent lack of adjacent hydroxyl groups, may be cleaved by lead tetraacetate if the proper solvent is employed. Experiments have shown that oxidation occurs only after formation of a vicinal hydroxyl pair. The formation of such "pseudo-glycols" takes place by addition of water, alcohol (methyl, ethyl, benzyl) or hydrocyanic acid to the keto group of the compound. The mechanism has been postulated as follows:

I.



$$\geq C-\underset{\overset{\|}{O}}{C}-\underset{\overset{|}{OH}}{C}=O + RH \longrightarrow \geq C-\underset{\overset{|}{OH}}{\overset{R}{C}}-\underset{\overset{|}{OH}}{C}=O$$

II



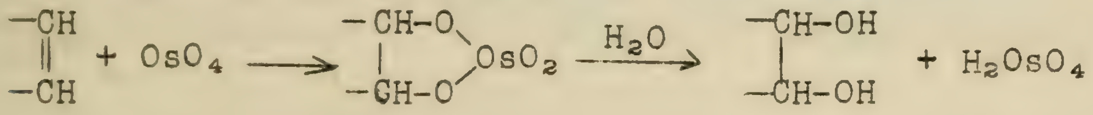
(R=HO-, CH_3O-, C_2H_5O-, $C_6H_5CH_2O$-, CN-)

Using water as the hydroxyl-forming component, Baer obtained a 74 per cent yield of pure benzoic acid from the cleavage of benzoin and a 50 per cent yield of mandelic acid from the cleavage of phenyl pyruvic acid.

This method of oxidative cleavage may be employed not only to determine α-keto acids quantitatively by the carbon dioxide evolved but also to distinguish them qualitatively from other keto-acids.

II. Osmium Tetroxide

The carbon-carbon double bond may be oxidatively "cleaved" to the glycol by a number of different reagents. The ethylene oxide formed by the effect of a peracid on cyclohexene generally yields upon hydrolysis the pure trans-diol, while oxidation by means of either dilute potassium permanganate or a chlorate on the presence of osmium tetroxide leads primarily to the isomeric cis-diol. Due to lack of sufficient explanations it must be assumed that the hydrolytic cleavage of the ethylene oxide undergoes a complete Walden Inversion, while in the latter cases, the formation of the cis-diol is thoroughly understandable. Boeseken postulates the following mechanism:



$$\begin{array}{l} -\mathrm{CH} \\ \ \| \\ -\mathrm{CH} \end{array} + \mathrm{OsO_4} \longrightarrow \begin{array}{l} -\mathrm{CH-O} \\ \ | \\ -\mathrm{CH-O} \end{array}\!\!> \mathrm{OsO_2} \xrightarrow{\mathrm{H_2O}} \begin{array}{l} -\mathrm{CH-OH} \\ \ | \\ -\mathrm{CH-OH} \end{array} + \mathrm{H_2OsO_4}$$

By the addition of osmium tetroxide to an equivalent amount of the olefine, Criegee has been able to isolate the osmic acid mono-esters of several compounds in excellent yields;

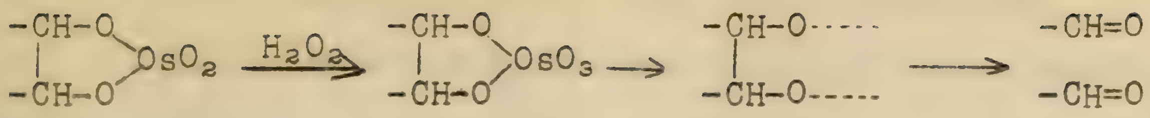
Olefine	Per Cent Yield of ester	m.p. °C(d)	State
Acenaphthylene	98	236	yellow needles
Indene	99	204	crystalline powd.
Δ_2-dihydronaphthalene	89	170	green leaflets
Δ_{9-10}-octalin	96	200	tan crystals

The diols may be obtained from the respective osmium-adducts in yields as high as 97 per cent.

During the past ten years Milas has utilized the osmium tetroxide method, with slight variations, in the preparation of many diols from the corresponding olefines. He carried out the reactions with hydrogen peroxide in tertiary butyl alcohol and a few cc. of 1 per cent oxmium tetroxide solution. The following may serve as examples:

ethylene	------	ethylene glycol,	93% yield
propylene	------	propylene "	68 "
styrene	------	phenyl "	50 "
cyclohexene	------	cis-cyclohexane diol,	58 "

In many cases the glycol formed simply plays the part of an intermediate whereby direct cleavage of the double bond occurs. This cleavage is assumed to follow the lead tetraacetate cleavage mechanism. In this case the stable osmium tetroxide-adduct with hexavalent osmium is oxidized under mild conditions with ethereal hydrogen peroxide to a compound with octavalent osmium which then spontaneously decomposes according to the equation:



Often undesired side reactions interfere but if the double bond lies adjacent to a benzene nucleus, the yields are very satisfactory. Criegee obtained a 77 per cent yield of benzaldehyde from stilbene in this manner.

Therefore, in the direct cleavage of carbon-carbon bonds by either lead tetraacetate or osmium tetroxide, it appears necessary to produce first a 1,4-biradical which then spontaneously decomposes into two fragments. In saturated compounds this can occur through suitable dehydrogenation of the glycol and in unsaturated compounds by the addition of oxygen-containing oxidizing agents.

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Reported by R. C. Gunther
October 9, 1940

DEGRADATION OF LONG CHAIN MOLECULES

H. Mark and R. Simha - Columbia University

I. Introduction

The work to be described is of interest because of the light it sheds on two problems; mechanism of reaction during polymerization, and the relation of molecular weight distribution to properties of polymers. In the past few years it has been possible to work out a reaction scheme for chemical or thermal decompositions involving many steps, each step being characterized by a definite activation energy and frequency constant. In particular, the degradation of chain molecules through the breaking of certain linkages in them has been followed by quantum mechanical observations. However, the dynamical treatment does not lend itself to the case of large particles, where it is far too complicated, and a statistical analysis promises some success, especially with large chain molecules, if certain conditions prevail.

The peculiarities of high polymers are due to the fact that they are very large. All synthetic and most natural polymers are non-homogeneous mixtures of chemically similar molecules which in size are distributed about a mean, some being much larger than the average and some much smaller. To understand adequately the fundamental nature of polymeric substances, we must know the molecular size distribution as well as the empirical composition and average molecular weight.

At present, the ultracentrifuge affords the only direct method for obtaining data on molecular size distribution but this equipment is costly and its use is not widespread.

Theoretical calculation of molecular size distribution is possible if the kinetics of the polymerization process is sufficiently well understood. Such calculations have been made by Flory and will be summarized later.

Several years ago, Hopff, Meyer and Mark found that the hydrolytic degradation of starch can be followed fairly accurately by assuming that all hydrolyzable bonds in the polymer are broken during decomposition at about the same rate, and that the total process can be calculated by a comparatively simple equation. Freudenberg and Kuhn later found during the degradation of cellulose under various conditions, that the best agreement of theory with experiment occurred when it was assumed that all the links of a long chain opened at the same rate, except a few links at each end of the chain.

Flory's calculations on polymerization bring out the fact that if one starts with a completely homogeneous material, for example, with N̲ chains each having n̲ links, the distribution curve

for the material is entirely sharp. If the product of degradation is composed altogether of monomers, we have present *N*·*n* monomers having an entirely sharp distribution curve as was the case of the original polymer. Intermediate between these two extremes of homogeniety however, the system is very heterogeneous, with respect to chain length, as is true in the case of much simpler types of decomposition involving molecules, radicals, atoms, etc.

In order to obtain more quantitative information about the heterogeniety existent during polymeric degradation, and indeed during polymerization, large quantities of homogeneous polymers of various types were prepared by Mark and Simha at the First Chemical Laboratory in Vienna, and certain of these, notably cellulose acetate polymers, were then degraded hydrolytically and the distribution curve followed quantitatively.

To compare experimental results with the theoretical behavior, it was necessary to use the expressions deduced by Kuhn and by Flory which were derived upon the assumption that the chain length of high polymers was infinite and that the breaking or making of a single link was inconsequential, conditions not holding here. Simha improved the theoretical treatment of the degradation reaction by taking into account the original chain lengths, and thus made possible the calculation of the relative amounts of larger chains during the early stages of degradation.

II. Statistical Formula

Flory has derived an expression for the weight distribution of molecular size for bifunctional condensations of the type,

$$A + A \rightarrow A\text{-}A$$

$$2A\text{-}A \rightarrow A\text{-}A\text{-}A\text{-}A$$

$$A + A\text{-}A \rightarrow A\text{-}A\text{-}A$$

or

$$A + B \rightarrow A\text{-}B \quad \text{etc.,}$$

always involving the same functional groups. The treatment rests upon the assumption that the reactivity of the functional group is not influenced by the size of the molecule to which it is attached. If *p* is the degree or extent of reaction of the monomer, $\bar{P}$ the degree of polymerization, and $F_{\bar{p}}$ the fraction of units present as $\bar{P}$-mers, then,

$$F_{\bar{p}} = \bar{P}\, p^{(\bar{P}-1)}(1-p)^2$$

If $F_{\bar{p}}$ is plotted against *p* for several stages of polymerization, it is evident that a wide distribution of species is present.

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[illegible]

[illegible]

III. [illegible]

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From Figure 1 it is obvious that $\bar{P}$ approaches infinity as $\underline{p}$ approaches 1, a condition not met in actual practice.

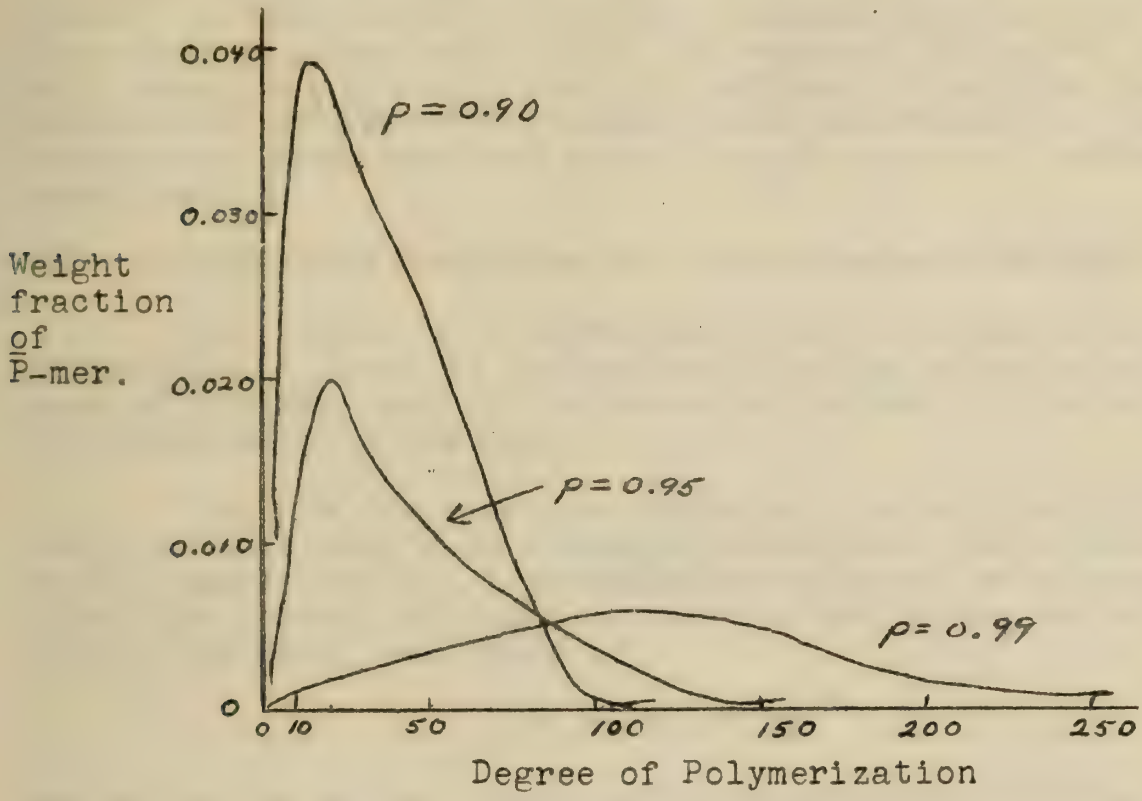

Figure 1

Weight Distribution of Molecular Size in Bifunctional Condensations

For the reverse process of degradation, we consider a chain of finite length, which when cut once has appreciably fewer links remaining, each of the remaining links then having a different probability of being attacked.

According to Simha, the probability of cutting out a single chain of $\underline{s}$ links from the original chain of $\underline{n}$ links, (i.e. the probability of creating a new molecule shorter than the high polymer), $\underline{s}$ and $\underline{n}$ being of the same order of magnitude, is given by the expression,

$$(1) \qquad P_s = \frac{r}{n}\left(\frac{n-r}{n-1} \cdot \frac{n-r-1}{n-2} \text{ ---- } \frac{n-r-s+1}{n-s}\right)\left(\frac{r-1}{n-s-1}\right)$$

where $\underline{r}$ is the total number of links opened.

Since a chain of $\underline{s}$ links contains $\underline{s+1}$ monomeric molecules, the total number of basic molecules contained in chains of $\underline{s}$ links is given by,

$$(2) \qquad N_{(s,r,n)} = \frac{r}{n}(r+1)\frac{(n-r)!}{(n-1)!}\;\frac{(n-s-1)!}{(n-s-r)!}\,(s+1)$$

This equation allows us to calculate the distribution curve of the molecular weight fractions at any given degree of decomposition $\frac{r}{n}$, if the length, n, of the original molecule is known. Each distribution curve represented by equation (2) gives N as a function of s when r and n are known. It offers, thereby an immediate possibility of direct comparison with experiment if distribution curves have been measured at different stages of degradation of a long chain.

III. Degradation Reactions and Their Comparison with Theory

The course of a degradation reaction can be followed fairly accurately if there is secured as starting material a highly homogeneous product, and if the reaction is carried out under mild and homogeneous conditions.

In this experiment a technical grade of cellulose called "cellite" was chosen as starting material. Its acetyl content was 39.3%, indicating 2-1/2 hydroxyls per glucose unit were acetylated. Using the characteristic constant for cellulose acetate in acetone derived by Obogi and Broda of

$$K_m = 9.0 \times 10^{-4}$$

the molecular weight was found to be about 110,000 by the viscosity method. This corresponds to a degree of polymerization, P, of about 410.

It was proven earlier by Obogi and Broda that fairly homogeneous samples of polymers could be obtained by dissolving in acetone and fractionally precipitating by addition of an acetone-water mixture. In this instance, 4000 g. of cellulose acetate was fractionated and 800 g. of this material which had an average degree of polymerization of 350, was selected for further work.

A sample of the starting material was itself fractionated and was found to be rather homogeneous since 82% of it had an average $\bar{P}$ = 340 while the overall average is 345. These facts are given in Table I.

Fraction	Size	$\bar{P}$	
1	7%	270	average $\bar{P}$ = 345
2	82%	340	
3	12%	400	

Table I

Initial Substance; $\bar{P}$ = 350 (Viscosity Method)

The material was then slowly degraded in an acetic acid-acetic anhydride mixture in which medium the reaction is homo-

geneous, a necessary condition for the validity of equation (2). One-fourth of the material was removed after twenty-four hours and the degradation of this part stopped by addition of water. After thorough washing and drying the sample was dissolved in acetone and fractionally precipitated to determine molecular size distribution. The remainder of the original was treated similarly at different stages of reaction and the results of fractionation of all four portions are listed in Table II. Again r is the number of links opened, and n the number of molecules in the original polymer, here equal to 350.

Deg. Prod.	P Ave. for Fract.	r	$\frac{r}{n}$	Fractionation Results % having $\bar{P}$				
1	158	1.2	0.0034	17-64	24-114	26-167	22-206	11-300
2	100	2.5	.0071	12-24	26-51	36-98	18-163	8-236
3	54	5.5	.0157	13-10	18-44	52-53	15-95	2-180
4	31	10.3	.0294	14-14	68-27	14-60	4-75	

Table II

Results of Fractionation After Different Reaction Times

These data are represented by Figures 2, 3, 4, and 5, in which the straight dotted lines represent experimental fractions as before, and the curves are smooth distribution curves based on the separate fractions.

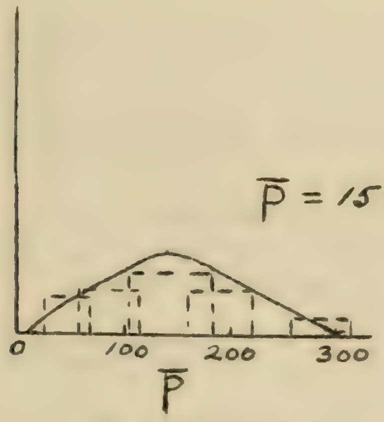

Figure 2

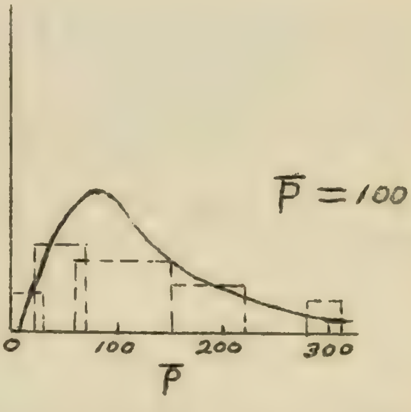

Figure 3

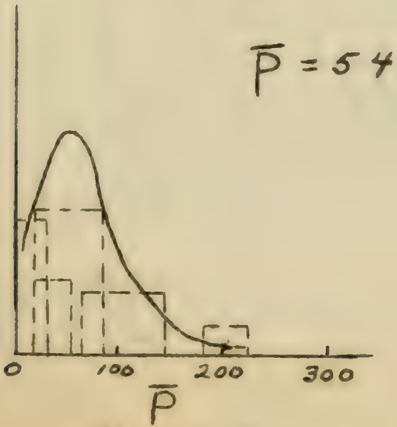

Figure 4

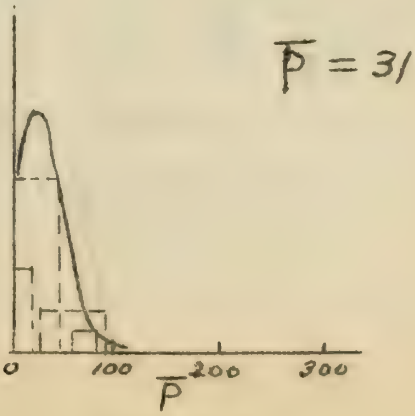

Figure 5

From these data it is evident that the first degradation product, which was treated for twenty-four hours, had an average degree of polymerization of 158, and that the product was highly heterogeneous, only 26% having an average $\bar{P}$ of 167 close to 158. The other fractions in the same relative amounts were even further removed from the mean as shown by the flat curve of Figure 2.

To apply these results to equation (2) in which we attempt to calculate the total number, Ns, of monomers in chains of s units, i.e of degree of polymerization equal to s, we must know s (or $\bar{P}$), r and n. As discussed above, n is $\bar{P}$ for the original substance, equal to 350 in this case, while r is obtained by dividing 1/2n, the number of original links, by the average $\bar{P}$ for any particular degradation product. s = $\bar{P}$ for any particular fraction of a degradation product for which we wish to calculate Ns.

A plot of equation (2) for degradation product 1 gives a curve which corresponds to a fair degree with the experimental curve. In the same way three other theoretical curves may be drawn, each coccesponding rather nicely to the experimental curves for degradation products 2, 3 and 4.

IV. Conclusion

From these curves it is obvious that the further the degradation proceeds, the sharper the molecular size distribution curve becomes.

Although the agreement of equation (2) with experiment is not quantitative, the relationship has good qualitative values and thereby indicates its usefulness in regulating the properties of polymers through knowledge of molecular size distribution.

The application of equation (2) depends upon the assumptions of homogeneous starting material, and of mild and homogeneous conditions during degradation.

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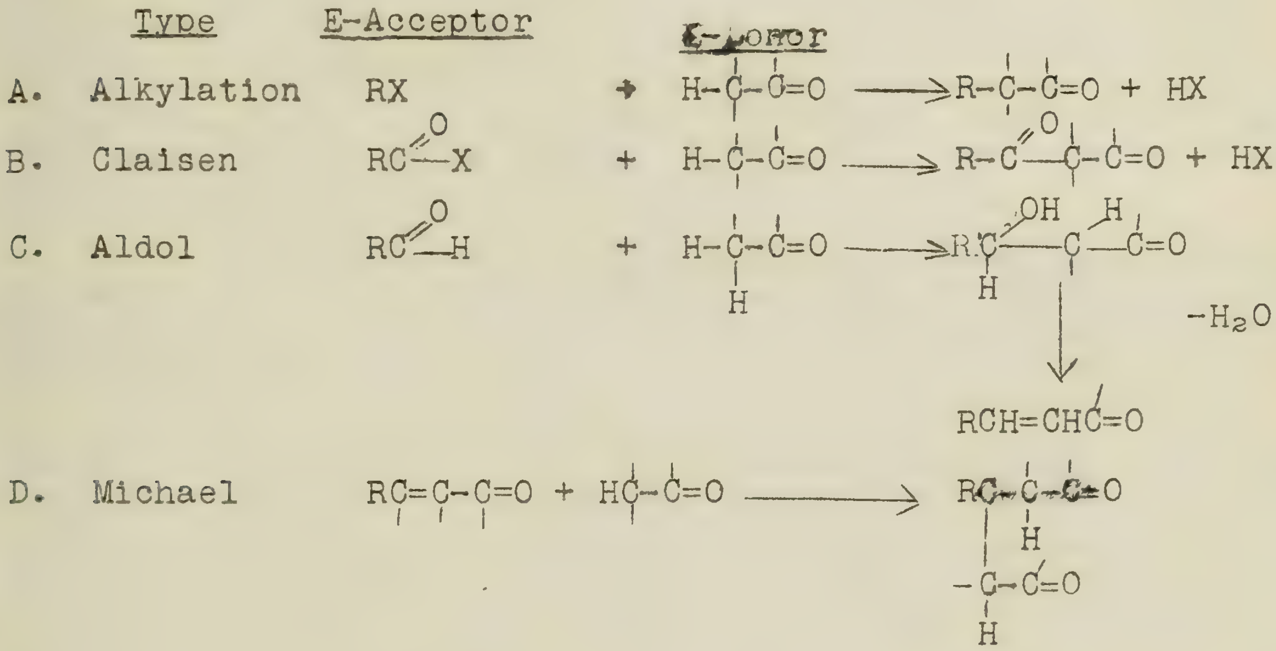
Reported by J. W. Kneisley
October 9, 1940

CONDENSATIONS EFFECTED BY ACIDIC AND BASIC REAGENTS

Hauser - Duke University

During the past three years, Hauser has published twelve articles on condensation reactions; ten of the articles covering condensation in basic media, and the last two on condensation effected by acidic substances. With one or two exceptions, condensations of the latter type are of comparatively recent development. Hauser proposes a general theory to cover analogous reactions under the two opposite conditions.

All condensations studied are alike in that the reaction is one between an electron donor and an electron acceptor. The four classes follow:



A. The condensation of any aklyl halide with acetoacetic ester in the presence of sodium ethoxide is a well known alkylation. In addition, we can now add BF_3 as a catalyst in this type for the same ester has been alkylated in its presence with benzylchloride.

B. If the X of $R\overset{O}{\overset{\|}{C}}{-}X$ is a $O\overset{O}{\overset{\|}{C}}{-}R$, OR, or Cl and the donor is a ketone or an ester, we have the reactants of the Claisen condensation. Using BF_3 in place of sodium ethoxide or sodium triphenylmethyl, Meerwein and Vossen have caused acetic anhydride to condense with acetophenone to give benzoylacetone.

C. Aldol condensations are considered to include in addition to the ordinary aldol, the Perkin and the Knoevenagel reactions. In contrast to the other types, acid catalyzed reactions are rather familiar here. Mesityl oxide and mesitylene from acetone

in the presence of sulfuric acid are standard preparations. Using an acidic catalyst, the authors have more recently condensed benzaldehyde with both malonic ester and acetophenone. The Perkin analogue was run in low yield.

D. When an active methylene compound is added to a double bond conjugated with a carbonyl, we have the Michael condensation. Again using BF_3, the authors condensed chalcone with malonic ester to give one of the products previously isolated from the base catalyzed reaction.

The theory proposed by Hauser is of a dual nature. In base catalyzed reactions he assumes the formation of an enolate of the electron donor as an activated intermediate.

For acid catalyzed reactions, he assumes a complex formation including the electron acceptor. Evidence presented by Price can be explained only by the presence of $BF_3 \cdot ROH$ complexes. Snyder has actually isolated a $ArCH=NAr \cdot BF_3$ complex. It is assumed that the tendency for ionization (or in some cases polarization) is increased due to the weakening of the bonds as a result of the attachment of BF_3 or $AlCl_3$.

The theory does not say that the reactivity of an acceptor is unaffected by the base or that the donor is exactly the same as though no acid were present. Such effects would exist but would be of a secondary nature.

A prediction based upon this theory is that in acidic media a donor must have at least a certain threshold activity in order for reaction to take place. Stated differently, this is to say that any series of donors will condense with any given acceptor in proportion to their respective abilities to ionize a proton. Experimental data on the successive condensation of benzaldehyde with ethyl acetate, acetic anhydride, acetophenone and malonic ester bear this out.

Further confirmation is found in the fact that methyl ketones will condense with benzalaniline while less active proton donors fail to do so.

A second prediction based upon this theory is that ethers too weakly ionized to be acceptors in basic media, should condense with ethylacetoacetate in the presence of BF_3. Isopropyl ether yielded a condensation product with the ester in 70-80 per cent yield. Under the same conditions, the alcohol yielded 40 per cent of the same product.

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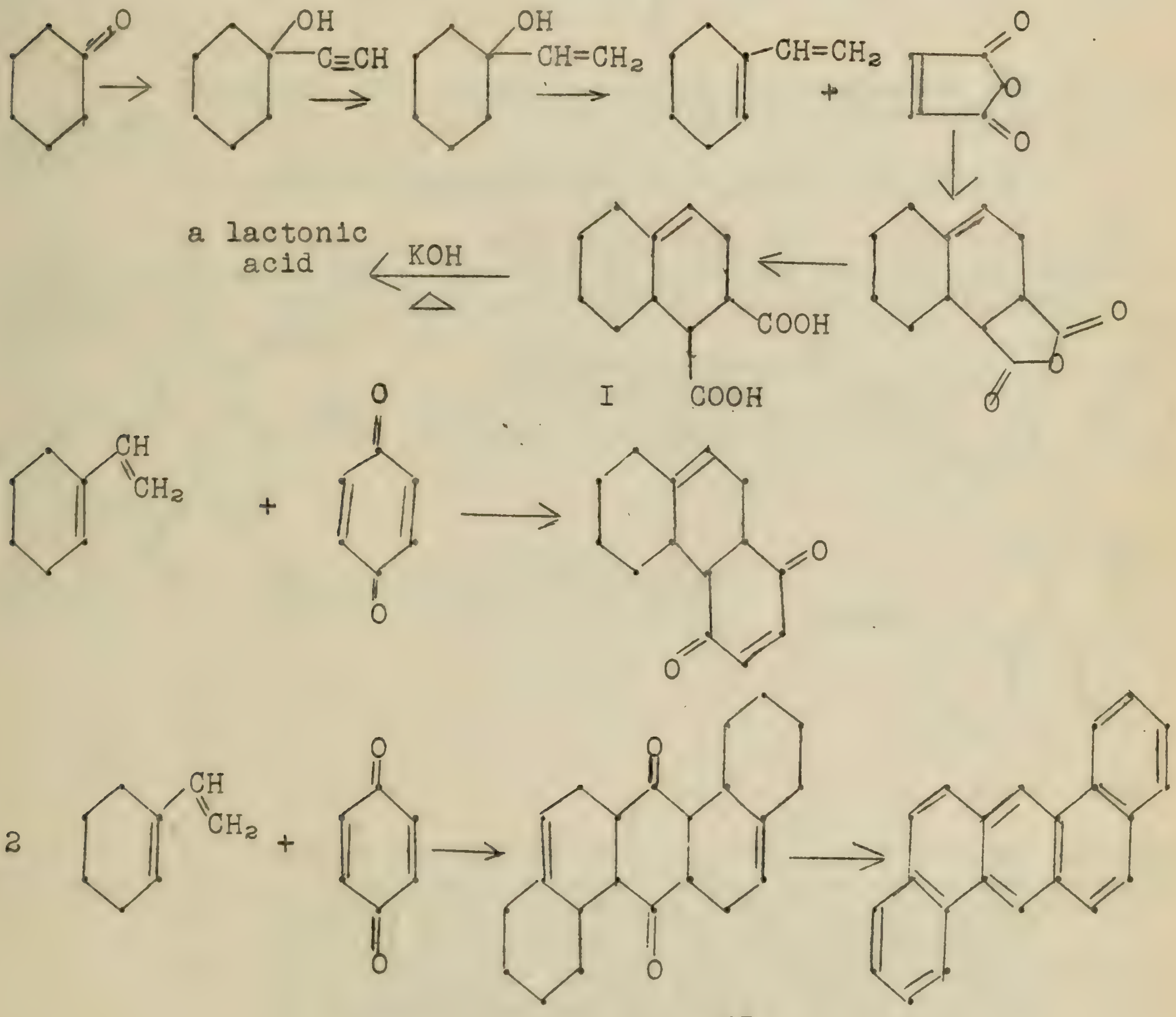
Reported by J. C. Robinson
October 16, 1940

APPLICATION OF THE DIELS ALDER REACTION
TO THE SYNTHESIS OF CONDENSED RING COMPOUNDS

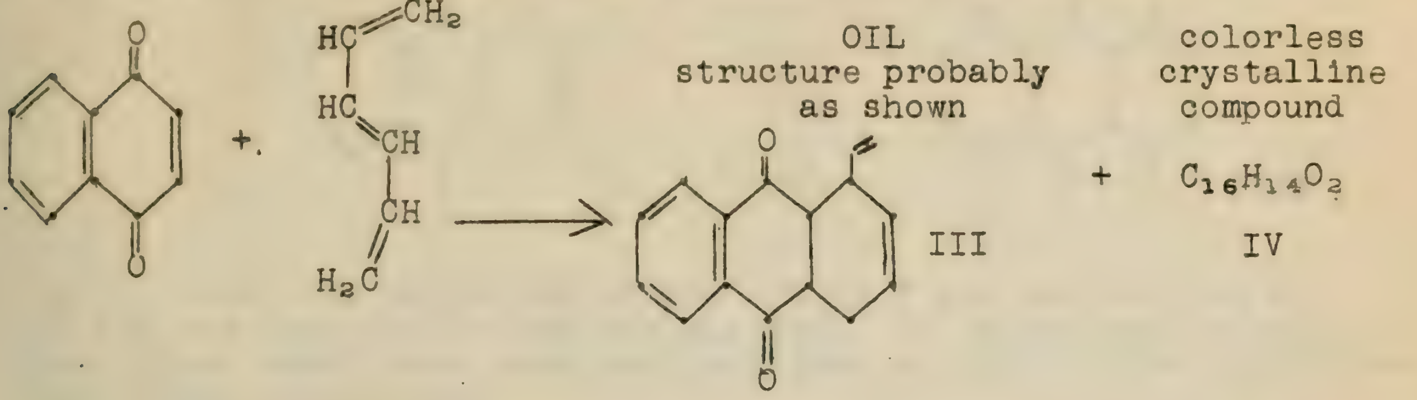
Of the important class of compounds, the non-benzenoid steroids, none had been totally synthesized prior to this year. In general, isomers arose to complicate the direct and simple syntheses. The Diels Alder reaction, however, presented a promising field in this respect because of the stereoselective manner in which it proceeds. Indeed, it usually gives a solid crystalline product that consists of a single isomer. In 1938, Cook and Lawrence investigated the additions of p-benzoquinone and maleic anhydride to 1-vinyl-1-cyclohexene:



II

The reactions with benzoquinone were controlled by the conditions and the amounts of reactants. The stereochemistry of product II was not investigated, but since a single crystalline product was obtained, one of the possible isomers must have been greatly favored in the reaction.

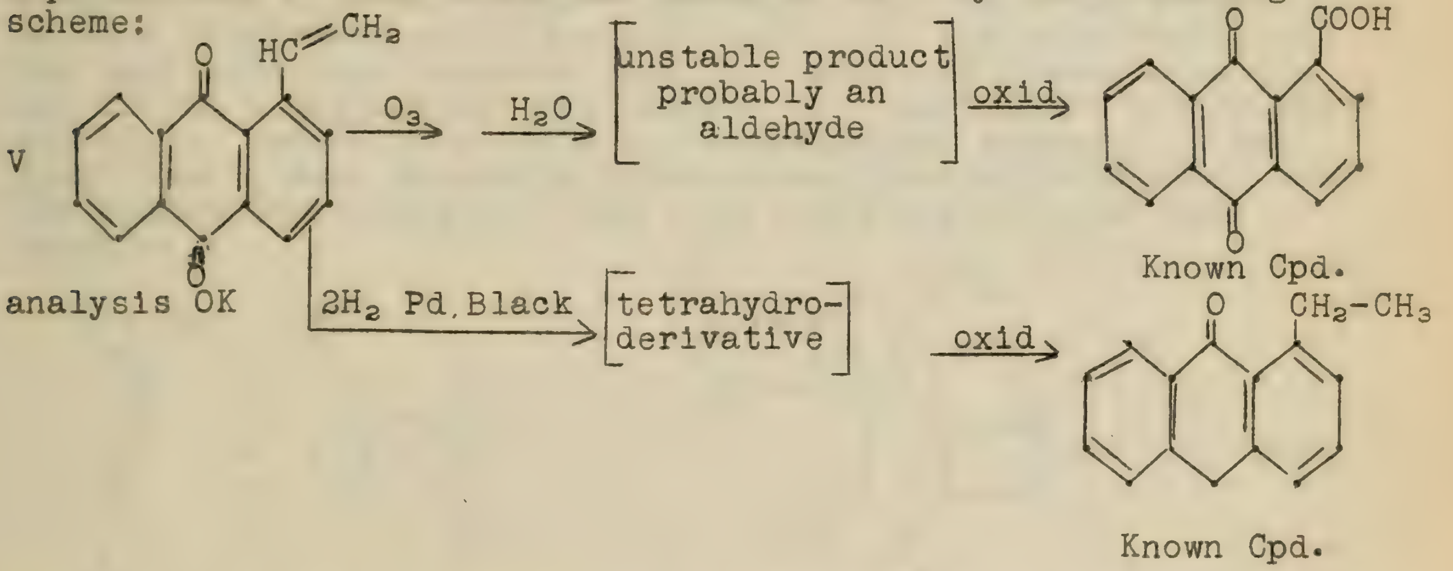
More recently Butz and coworkers have extended the investigation to cases where six-carbon-conjugated-systems replaced the dienes. In an early attempt hexatriene was employed:



Structure III probably represents correctly the nature of the main portion of the oil as indicated by the following evidence:

1. Analysis corresponds to $C_{16}H_{14}O_2$ (OK for III).

2. On treatment with alcoholic KOH a red enolate is formed which was easily oxidized to a yellow crystalline solid of m.p. 163-164°. This solid was shown to be V by the following scheme:



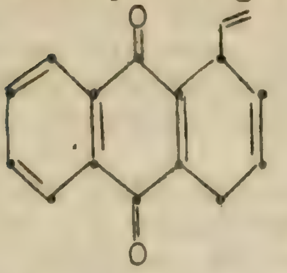
3. On heating the oil at 200-236° under 2.5 mm. pressure for some time, a change took place. Three products were isolated:

a. A nearly colorless cyrstalline compound which was oxidized to compound IV by ferric chloride.

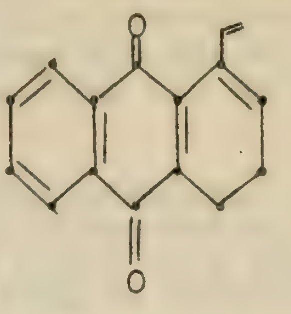
b. An oil which no longer gave the red enolate and was not oxidized by air in the presence of potassium hydroxide to any insoluble product such as V.

c. After standing in air for some time a 50% yield of a yellow crystalline substance, $C_{16}H_{12}O_2$, which was different from V and depressed sharply the melting point of an authentic sample of 1-ethyl-9,10-anthraquinone. It contained a vinyl group because it was

oxidized though not too readily to V. This product was probably VI, the only other reasonable possibility being VII.



VI

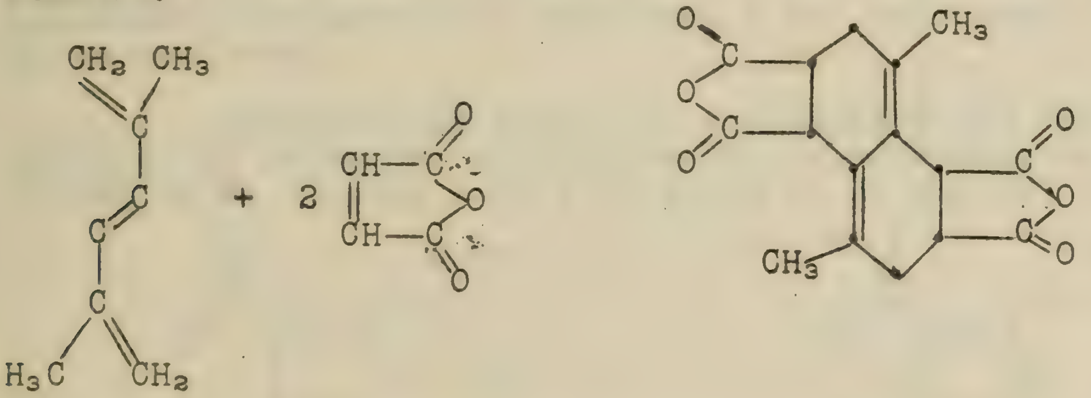


VII

4. The oxidation of the oil to V was carried out at 30° and was complete in fifteen minutes. It is improbable that a vinyl group would have been produced from an ethyl or an ethylidene under these conditions.

5. The structure of the solid product IV was elucidated. It was an isomer of III whose formation as well as the formation of the nearly colorless derivative, mentioned in 3 (a) above, can be explained on the assumption that an impurity was present in the hexatriene used.

It is noted that all evidence obtained pointed to the formation of only one product (probably III) from the addition of pure hexatriene and 1,4-naphthoquinone. The continuation of the synthesis then depended upon the chance of isomerizing the oil III to a conjugated type capable of a particular second diene addition. Before this could be investigated, however, it was found that a more promising reaction was available starting from the symmetrical dienynes. Two such reactions have now been studied:



VIII

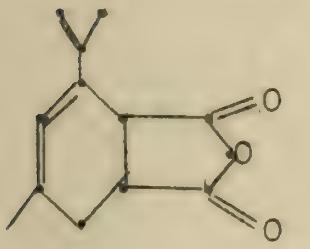
Structure VIII is not beyond doubt --- particularly with regard to the location of the double bonds:

The product analyzed properly; it hydrolyzed to a tetrabasic acid; it added the right amounts of Br_2 and H_2; it reacted with $KMnO_4$; and it dehydrogenated to the expected 1,5-dimethyl-naphthalene (which was confirmed by synthesis). The location of the double bonds as conjugated and heteronuclear is based on ultraviolet absorption. It is not conclusive because no 1,2,3,5,6,7

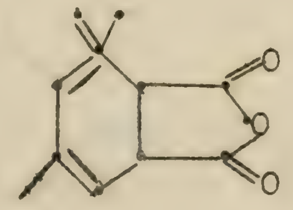
hexahydronaphthalene was available for comparison. Other types which were compared contained heteronuclear conjugated systems, intranuclear-conjugated systems and conjugated ethylene-carbonyl-systems. Only the first of these corresponded.

Product VIII was easily obtained in crystalline form and an investigation is under way at the present to determine its stereochemical nature. As written, it could exist as a *meso*-or a *dl*- form. This will give new light on the mode of addition of maleic anhydride if successful.

A study of the manner in which the product could have been formed led to some interesting possibilities. An intermediate of structure IX is considered to be possible since Favorskii has discovered that 1,2-heptadiene is stable enough to be isolated.



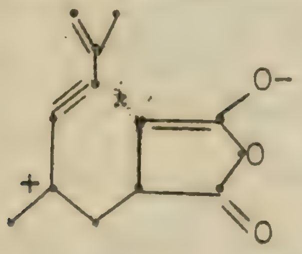
IX



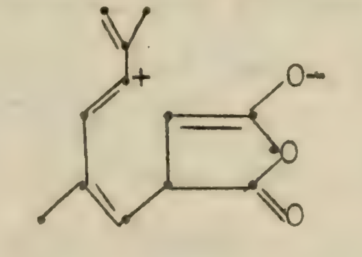
X

Thus, IX might be capable of existing long enough for the reaction to proceed by way of addition of a second mole of anhydride or shift to an intermediate of structure X. However, none of the substance represented by structure X has ever been obtained from these mixtures.

Robinson has suggested a mechanism for the Diels Alder addition in which the intermediates are activated forms. If this mechanism is applied here such forms as XI and XII are postulated:

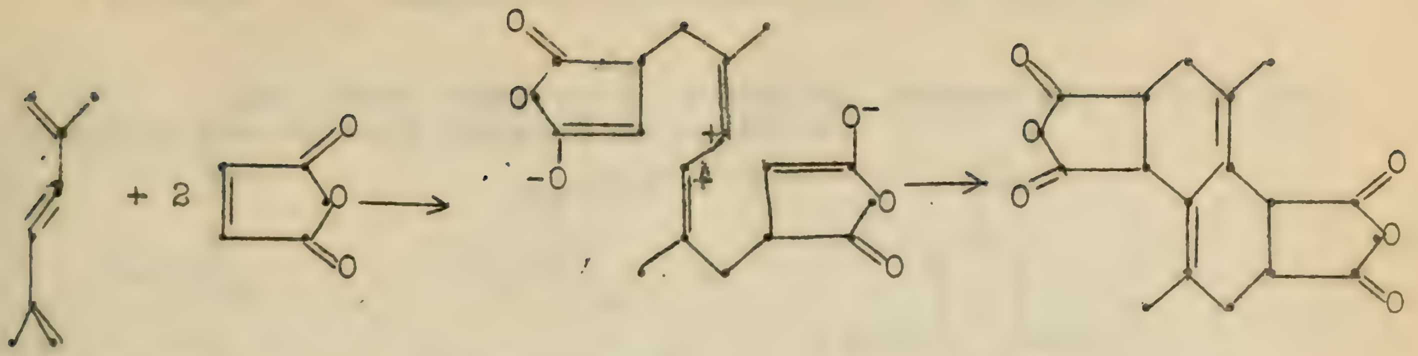


XI

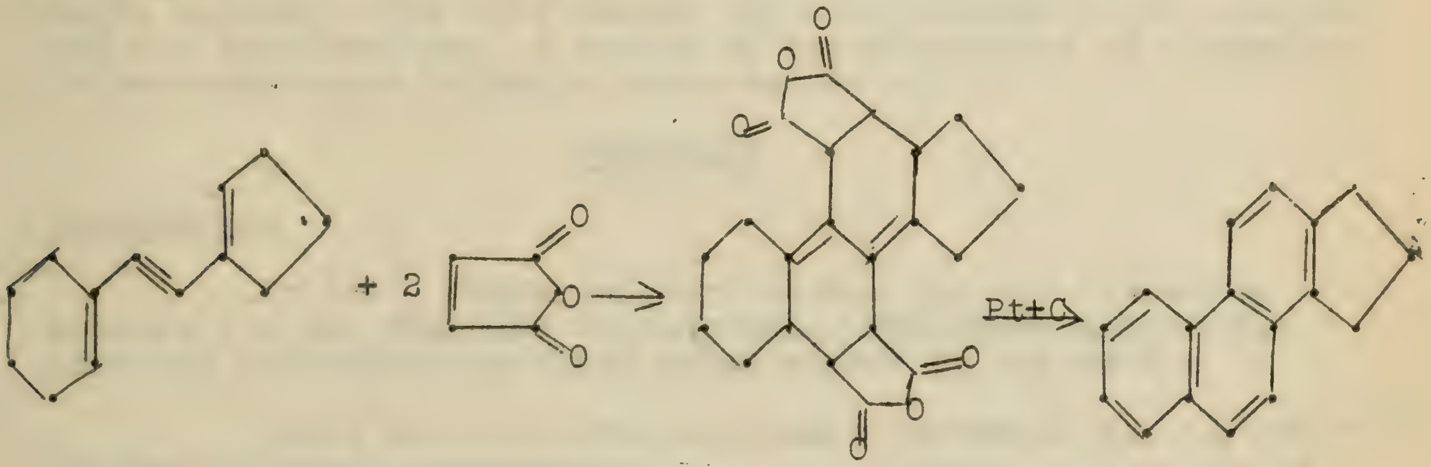


XII

This mechanism is capable of many variations, depending upon whether the yne or the ene adds first and the time when migration of hydrogen occurs. It is also possible that two moles of anhydride are added at the same time, in which case it is unnecessary to postulate the migration of hydrogen:



Finally, in April 1940, a communication to the editor announced that Butz and coworkers had effected the total synthesis of a non-benzenoid steroid:



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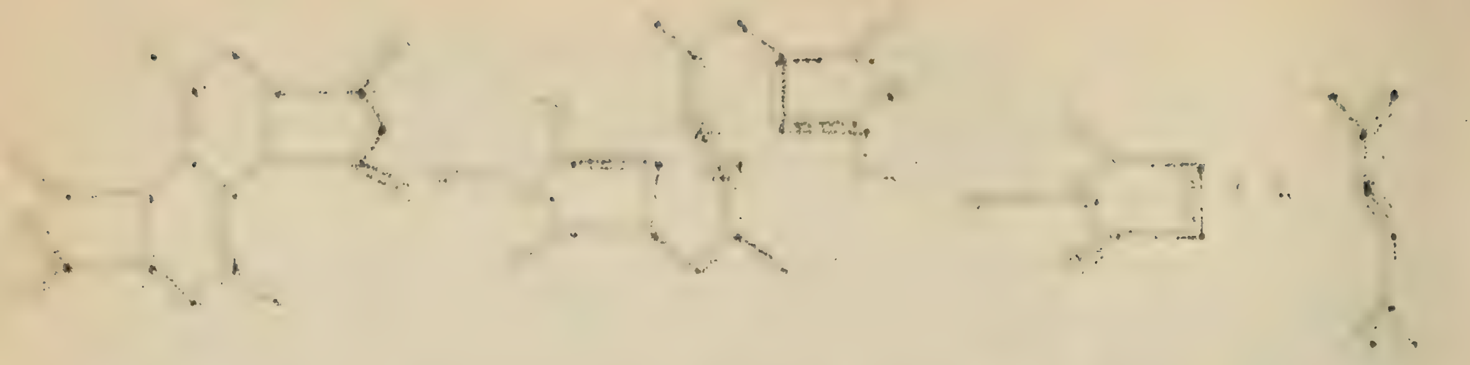
Reported by W. L. Walton
October 16, 1940



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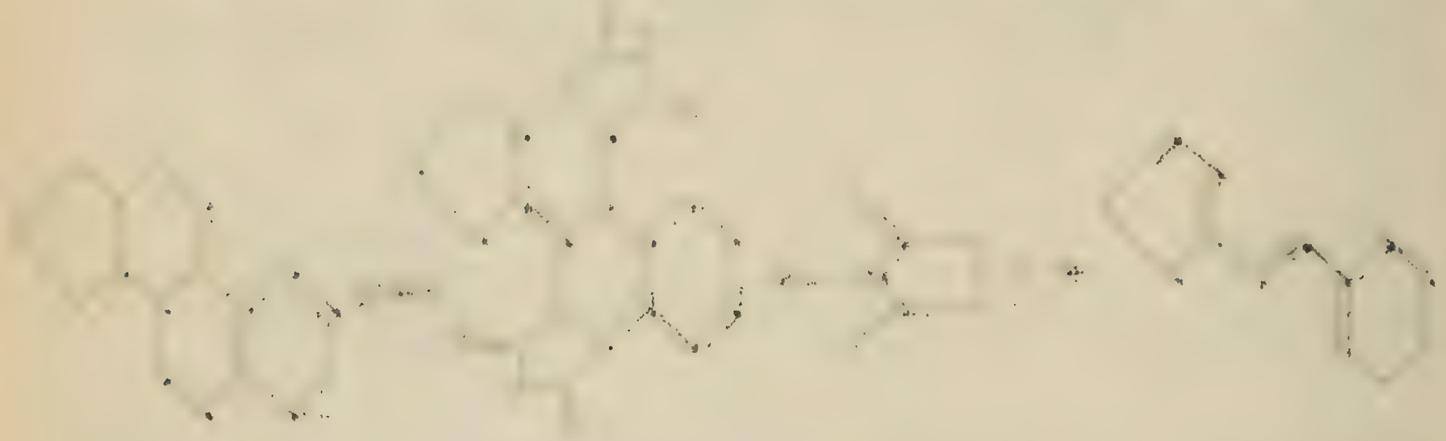

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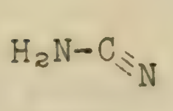
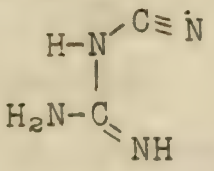
A REVIEW OF CYANAMIDE, DICYANDIAMIDE, AND MELAMINE

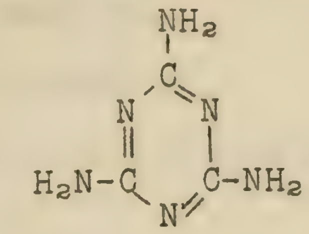
The three compounds, melamine, cyanamide, and dicyandiamide are closely related as is shown:



cyanamide
(monomer)



dicyandiamide
(dimer)



melamine (trimer)

In the last few years their commercial development has advanced quite rapidly. For this reason and also because these compounds are not very familiar, a review of the properties of cyanamide, dicyandiamide and melamine seems warranted.

CYANAMIDE

Preparation

In 1897, Frank and Caro worked out the cyanamide process for the fixation of nitrogen. The calcium cyanamide produced furnished the first cheap source of cyanamide.

Early methods used to prepare cyanamide are illustrated by the following equations:

$$H_2N\text{-}C\text{=}NH\text{-}NH_2 \xrightarrow{KOH} H_2N\text{-}CN + NH_3$$

$$H_2N\text{-}CO\text{-}NH_2 \xrightarrow{SOCl_2} H_2N\text{-}CN + H_2O$$

$$Cl\text{-}CN + NH_3 \longrightarrow H_2N\text{-}CN + HCl$$

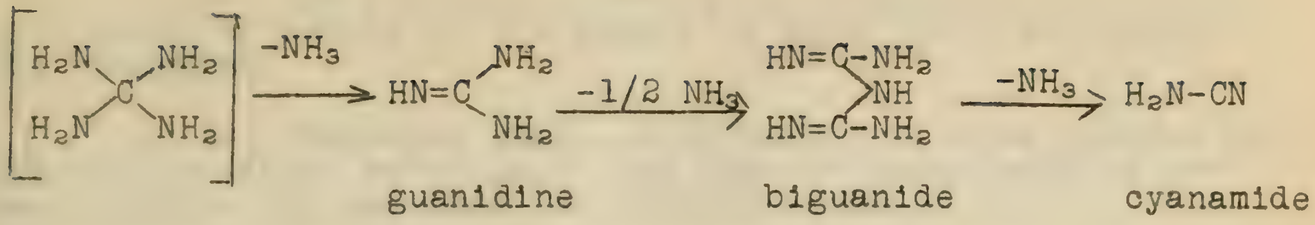
These methods are of no practical value. The method now used for preparing cyanamide by the American Cyanamide Company is the addition of sulfuric acid to a solution of calcium cyanamide in order to precipitate calcium sulfate:

$$CaCN_2 + H_2SO_4 \longrightarrow H_2N\text{-}CN + CaSO_4$$

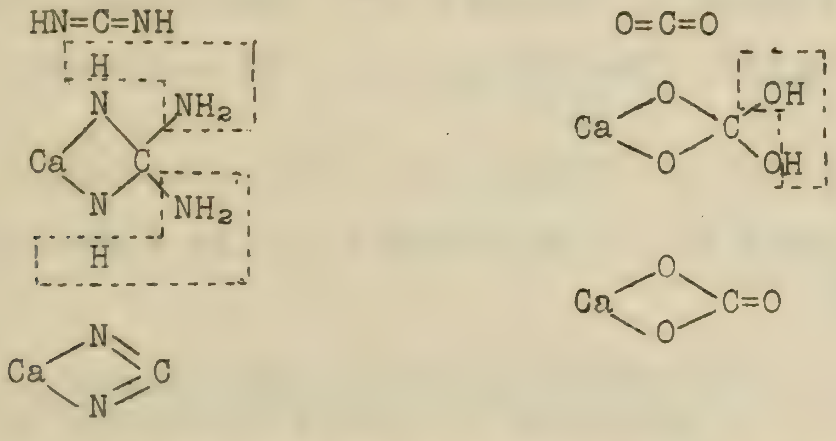
A pH of 5 must be maintained and the temperature is held below 30°.

Properties:

Franklin, in 1922, pointed out that cyanamide is the analog in the ammonia series of carbon dioxide and that products related to cyanamide may be considered deammonation products of a hypothetical ammono-o-carbonic acid:



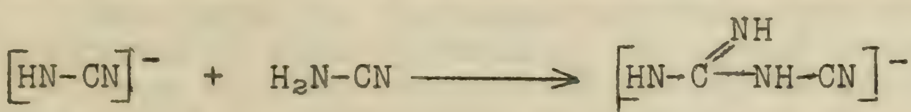
The analogy between the carbonates and the cyanamides can also be shown:



Cyanamide is a white, deliquescent solid melting at 41°. It is soluble in water, alcohol, and ether.

Cyanamide is quite unstable especially in aqueous solution due to a strong tendency to polymerize or hydrolyze. Probably the most important reaction is its polymerization to dicyandiamide, $H_2N-C=NHNH-CN$. The principal facts concerning this reaction may be summarized:

1. The polymerization of cyanamide to dicyandiamide involves a second order reaction of a cyanamide ion with a cyanamide molecule. The product combines with a proton.



$$[HN-CN]^- + H_2N-CN \longrightarrow [HN-\overset{NH}{\overset{\|}{C}}-NH-CN]^-$$

2. The rate of polymerization is a function of the hydrogen ion concentration. The maximum rate is at pH 9.6 and the rate decreases rapidly above or below this point. Above pH 12, quantitative hydrolysis to urea occurs.

3. Small amounts of melamine are formed.

The hydrolysis of cyanamide to urea may be summarized as follows:

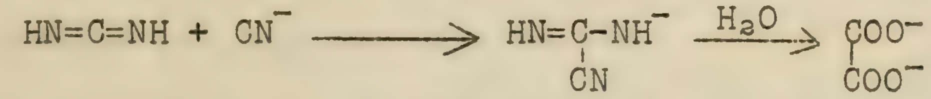
1. It is a reaction of the first order.

2. Cyanamide disappearing is quantitatively accounted for by urea formed.

3. The reaction velocity is independent of the concentration of alkali if the alkali is more than equivalent to the cyanamide.

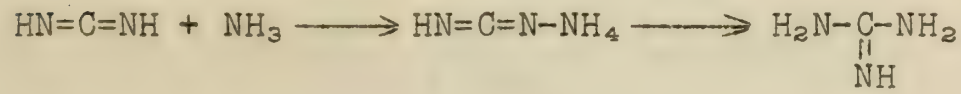
4. Cyanamide does not hydrolyze to urea between pH 4 and 10. However, below pH 4, the rate of hydrolysis is proportional to the hydrogen ion concentration.

When calcium cyanamide and calcium cyanide are autoclaved together, a yield of about 32% of the oxalate and 60% of the formate is obtained. The equation is thought to be ionic:



$$HN{=}C{=}NH + CN^- \longrightarrow HN{=}\underset{CN}{C}{-}NH^- \xrightarrow{H_2O} \begin{matrix} COO^- \\ | \\ COO^- \end{matrix}$$

Cyanamide reacts with ammonia to form guanidine.



$$HN{=}C{=}NH + NH_3 \longrightarrow HN{=}C{=}N{-}NH_4 \longrightarrow H_2N{-}\underset{\underset{NH}{\|}}{C}{-}NH_2$$

Hydrogen sulfide and cyanamide react to form thiourea. This is the commercial source of thiourea.

The last three reactions may be considered analogous to the corresponding reactions of aldehydes and ketones.

Cyanamide itself has no uses or applications but is the intermediate of many important compounds.

DICYANDIAMIDE

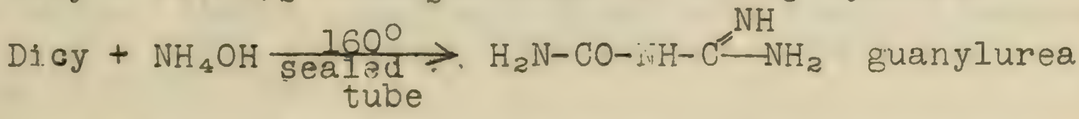
Dicyandiamide is a white solid melting at 207°. It is only slightly soluble in cold water and is practically insoluble in alcohol or ether.

Dicy which is the common abbreviation for dicyandiamide is always prepared from cyanamide. The usual procedure is to heat an aqueous solution containing cyanamide and from 2.5% to 4% ammonia until the conversion is complete. The yields are around 98%.

Chemical Reactions:

With alkalies:

1. Dicy + $Ba(OH)_2 \xrightarrow{\Delta} H_2N{-}CO{-}NH{-}CN + NH_3$ cyanurea

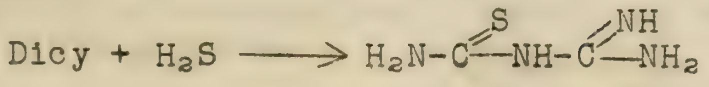


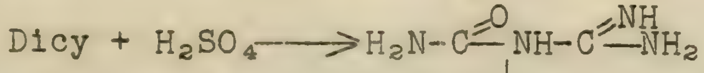
2. Dicy + $NH_4OH \xrightarrow[\text{sealed tube}]{160^\circ} H_2N{-}CO{-}NH{-}C{\overset{\displaystyle NH}{\lessdot}}NH_2$ guanylurea

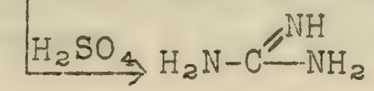
3. Dicy + $K_2CO_3 \xrightarrow{300^\circ} 4KOCN + 2H_2O$ potassium cyanate

4. Dicy + NaOH $\xrightarrow{330^\circ}$ $Na_2N\text{-}CN$ Sodium cyanamide

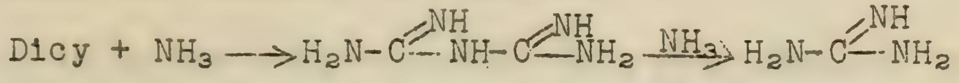
With acids:

1. 
$\mathrm{Dicy + H_2S \longrightarrow H_2N{-}C({=}S){-}NH{-}C({=}NH){-}NH_2}$ guanylthiourea

2. 
$\mathrm{Dicy + H_2SO_4 \longrightarrow H_2N{-}C({=}O){-}NH{-}C({=}NH){-}NH_2}$ guanylurea

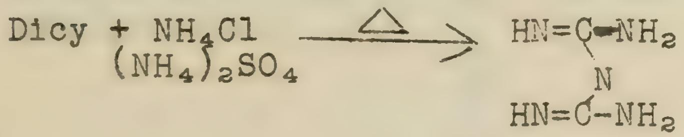

$\mathrm{\xrightarrow{H_2SO_4} H_2N{-}C({=}NH){-}NH_2}$ guanidine

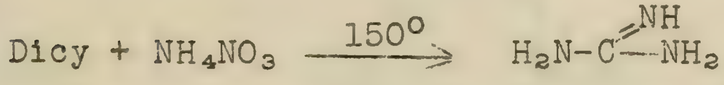
With ammonia and ammonia derivatives:

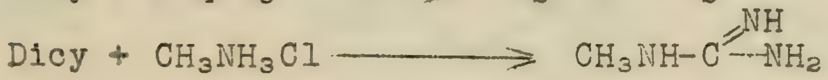
1. 
$\mathrm{Dicy + NH_3 \longrightarrow H_2N{-}C({=}NH){-}NH{-}C({=}NH){-}NH_2 \xrightarrow{NH_3} H_2N{-}C({=}NH){-}NH_2}$

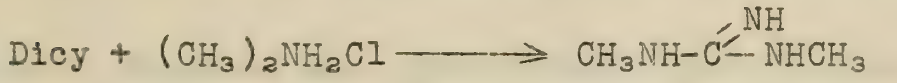
biguanide

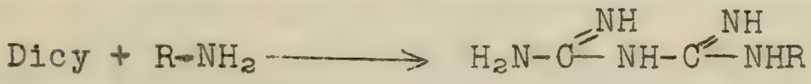
2. Dicy + liq.NH_3 $\xrightarrow[2\ \text{hrs.}]{150^\circ}$ melamine 80%

3. 
$\mathrm{Dicy + \begin{matrix} NH_4Cl \\ (NH_4)_2SO_4 \end{matrix} \xrightarrow{\Delta} \begin{array}{l} HN{=}C{-}NH_2 \\ \quad N \\ HN{=}C{-}NH_2 \end{array}}$ biguanide

4. 
$\mathrm{Dicy + NH_4NO_3 \xrightarrow{150^\circ} H_2N{-}C({=}NH){-}NH_2}$

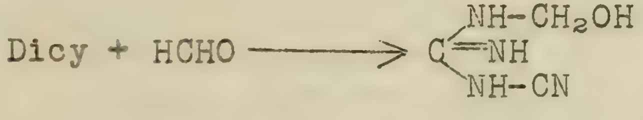
5. 
$\mathrm{Dicy + CH_3NH_3Cl \longrightarrow CH_3NH{-}C({=}NH){-}NH_2}$

6. 
$\mathrm{Dicy + (CH_3)_2NH_2Cl \longrightarrow CH_3NH{-}C({=}NH){-}NHCH_3}$

7. 
$\mathrm{Dicy + R{-}NH_2 \longrightarrow H_2N{-}C({=}NH){-}NH{-}C({=}NH){-}NHR}$

8. Dicy + urea ⟶ ammeline

Miscellaneous:

1. 
$\mathrm{Dicy + HCHO \longrightarrow C\begin{cases} NH{-}CH_2OH \\ {=}NH \\ NH{-}CN \end{cases}}$

2. Dicy + Zn + HCl ⟶ guanidine + CH_3NH_2

Dicyandiamide is important commercially in the production of melamine, guanidine derivatives, and certain pharmaceutical products such as barbiturates. To illustrate its growing importance: twenty years ago it was considered a comparatively rare chemical - today its price is eighteen cents a pound and it is sold in carload lots.

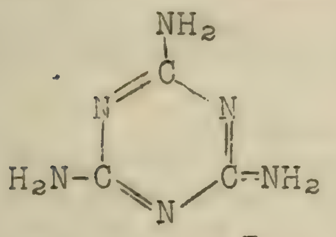
MELAMINE

Melamine, the trimer of cyanamide is one of the most recent additions to the field of important industrial chemicals. Less than two years ago, it was a rare chemical that could be obtained only in limited quantities and sold for forty dollars a pound. Today it is produced on a commercial scale and sells for about forty cents a pound.

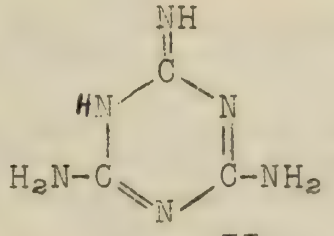
Melamine was first prepared in 1834 by Liebig who heated a mixture of potassium thiocyanate and ammonium chloride. Since that time there have been only occasional investigations of melamine until the last few years.

Structure

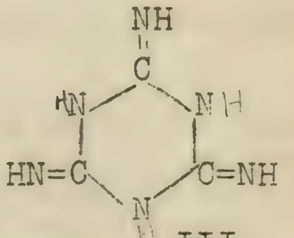
The structure most commonly used for melamine is I. This is usually designated as the amino structure since there has been considerable evidence pointing to the existence of an imino structure (III) at least under some conditions. It is also possible that the true structure is some intermediate (II) between the amino and imino structure or that an equilibrium exists among the various possibilities.



I

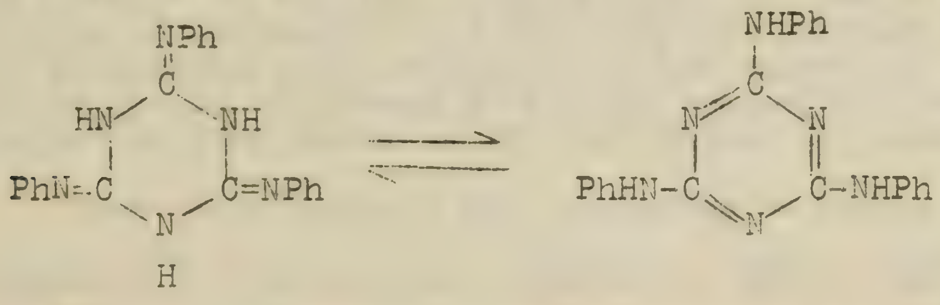


II

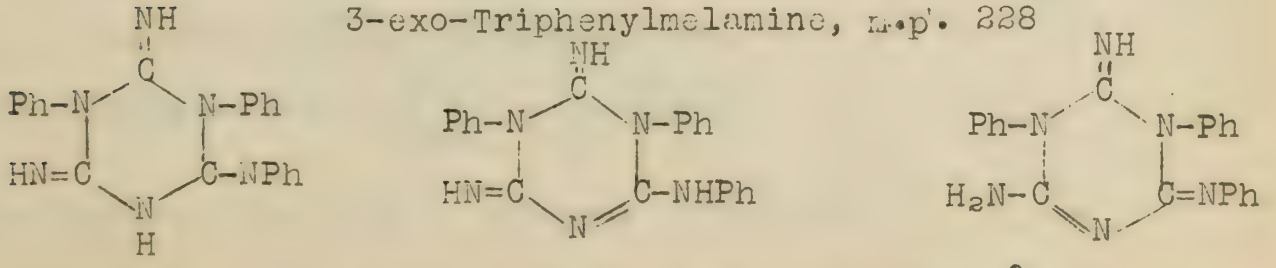


III

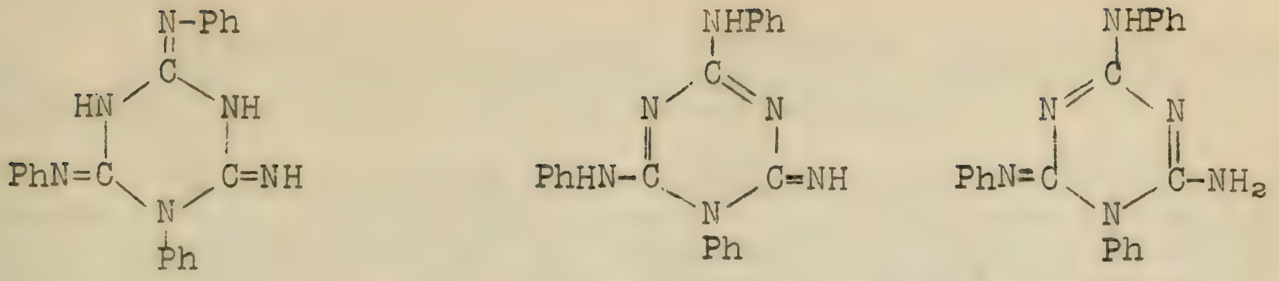
Rathke has done some interesting work on substituted melamines and has shown that the substituted melamines (amino structure) are distinctly different from the substituted isomelamines (imino structure). Rathke prepared four isomers of the triphenylmelamine series, the structures of which are given:



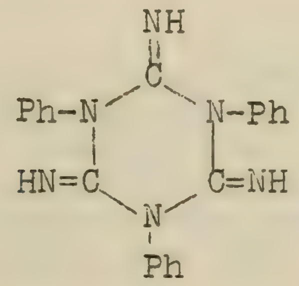
3-exo-Triphenylmelamine, m.p. 228°



2-eso-Triphenylmelamine, m.p.217°



1-eso-Triphenylmelamine, m.p. 221°



3-eso-Triphenylmelamine, m.p. 185°

As is shown all but one of the triphenylmelamines can tautomerize. The nomenclature was used by Rathke.

Hofmann in 1885 prepared some trialkyl melamines and iso-trialkylmelamines, so that the existence of the two series of substituted melamines is fairly well established. Little further work has been done to clear up the true structure of melamine.

Preparation:

On a large scale, melamine is always prepared from dicyandiamide. Most commercial processes involve the treatment of dicy and ammonia at elevated temperatures and under pressure. The reaction is exothermic and the temperature must be buffered in order to prevent polymerization of the melamine. Melamine is prepared in yields of around 90% . It is purified either by crystallization from water or by sublimation at reduced pressure.

Some other methods for preparing melamine are:

1. $NH_4SCN \xrightarrow{\Delta}$ Guanidine, Melamine, Melan, Melem, Melon
2. Guanidine $\xrightarrow{170^\circ}$ Melamine, etc.
3. Cyanuric acid $\xrightarrow[100^\circ C.]{NH_3}$ Melamine

These methods are only of academic interest.

Properties:

Melamine is a colorless crystalline solid which melts at 354°. It can be crystallized from water, is only slightly soluble in alcohol, and is insoluble in inert solvents.

Melamine is very stable chemically showing no tendency to decompose below its melting point. On heating above its melting point, ammonia is lost and the final product is melon which is stable at red heat. The course of this deammonation appears to follow the path: Melamine → melam → melem → melon.

Uses:

Melamine is used almost entirely for the production of resins. It is used in molding resins under the trade name, "Beetle-Melamine" and is showing great promise in this field largely because of its remarkable stability to heat and light. Melamine is also being incorporated in resins for surface-coating enamels and varnishes, under the trade name "Melamac" resins.

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Reported by S. B. Speck
October 23, 1940

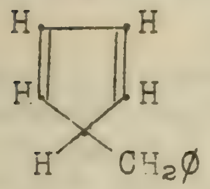
STUDIES IN THE CYCLOPENTADIENE SERIES

Alder - University of Cologne

Alkylated cyclopentadienes are useful compounds in connection with the Diels-Alder reaction, especially since they make possible the synthesis of bicyclic molecules of the camphor type. The products of such diene syntheses are of considerable stereochemical interest. Alkyl cyclopentadienes - together with the corresponding fulvenes - are present in gasolines produced by cracking.

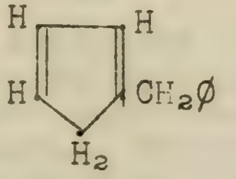
Although various monosubstituted cyclopentadienes have been known for a long time, no attempts have been made until recently to identify them as 1-, 2-, or 5-derivatives. In 1936, Alder commenced work upon this problem. Potassium cyclopentadiene, upon treatment with benzyl chloride, gave a monobenzylcyclopentadiene fraction as well as some of the dibenzyl derivative. Both products were formed in the dimeric state; however, they depolymerized conveniently to give the rather unstable monomers upon slow distillation in vacuo. The mono-fraction was found to be a mixture of two isomers, which could be separated by the difference in ether solubility of their adducts with maleic anhydride. The following structures were possible for the two monobenzylcyclopentadienes:

I



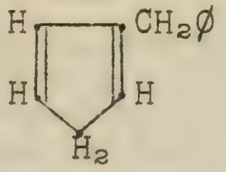
5-benzyl-

II



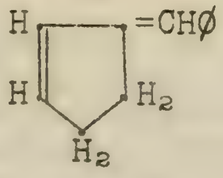
1-benzyl-

III



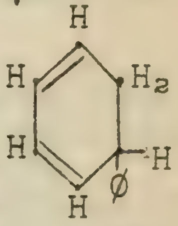
2-benzyl-

IV

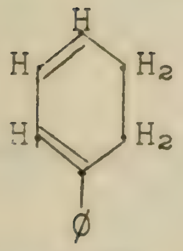


benzal-

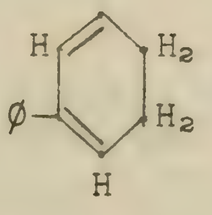
V



VI



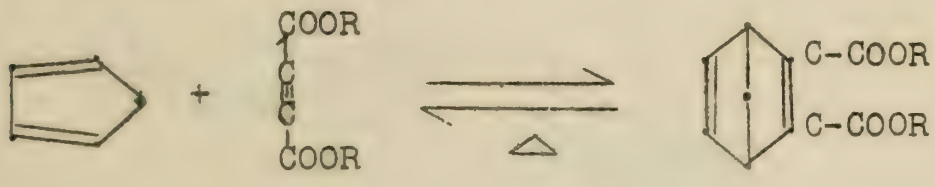
VII

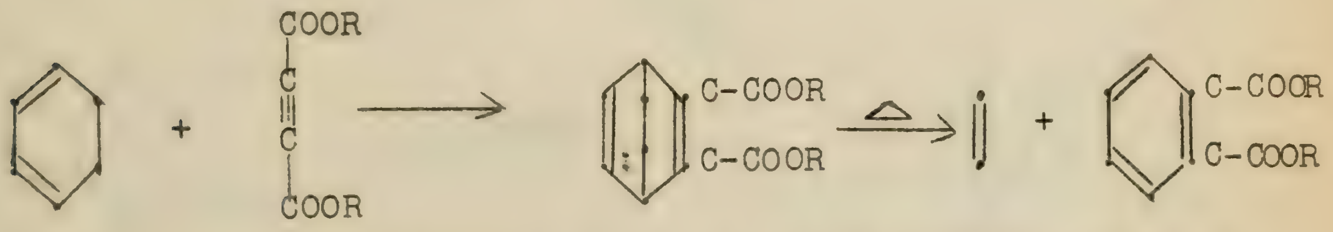


The possibility of 6-membered ring formation (V - VII) could not be ignored in view of the known reaction of such a compound as chloroform or benzal chloride on an alkali metal salt of pyrrol to give a pyridine derivative. However, the 6-membered ring structures were eliminated at once:

1. Dehydrogenation with selenium gave no traces of biphenyl.

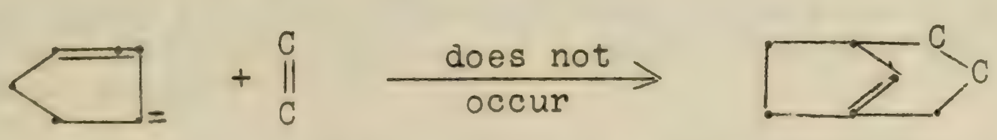
2. A general method was developed for distinguishing between cyclic penta- and hexadienes. Alder and Rickert found that the adduct formed between a cyclopentadiene and the diethyl ester of acetylene dicarboxylic acid may be distilled in vacuo either entirely unchanged or, if dissociation does take place, with immediate recombination, so that the distillate yields the original adduct. Identical treatment of a corresponding cyclohexadiene adduct gives an unsaturated hydrocarbon and o-phthalic acid or a derivative of it:



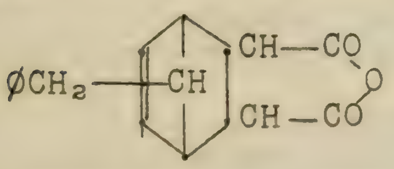


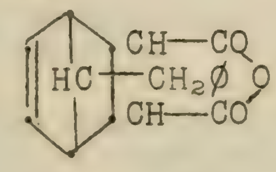
The monobenzylcyclopentadienes gave the characteristic reaction of a 5-membered ring.

Upon treatment with maleic anhydride, the monobenzylcyclopentadiene fraction gave a quantitative yield of crystalline adduct, separable into two constituents which proved to be structural isomers. Structure IV was therefore eliminated at once, since the diene synthesis does not proceed if the bicyclic combination which would result would have a double bond on the bridge head:



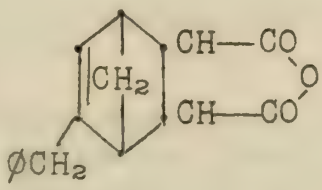
The possible structures of the two maleic anhydride adducts are as follows:





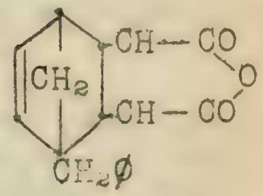
VIIIa VIIIb

from 5-benzyl-



IX

from 2-benzyl-



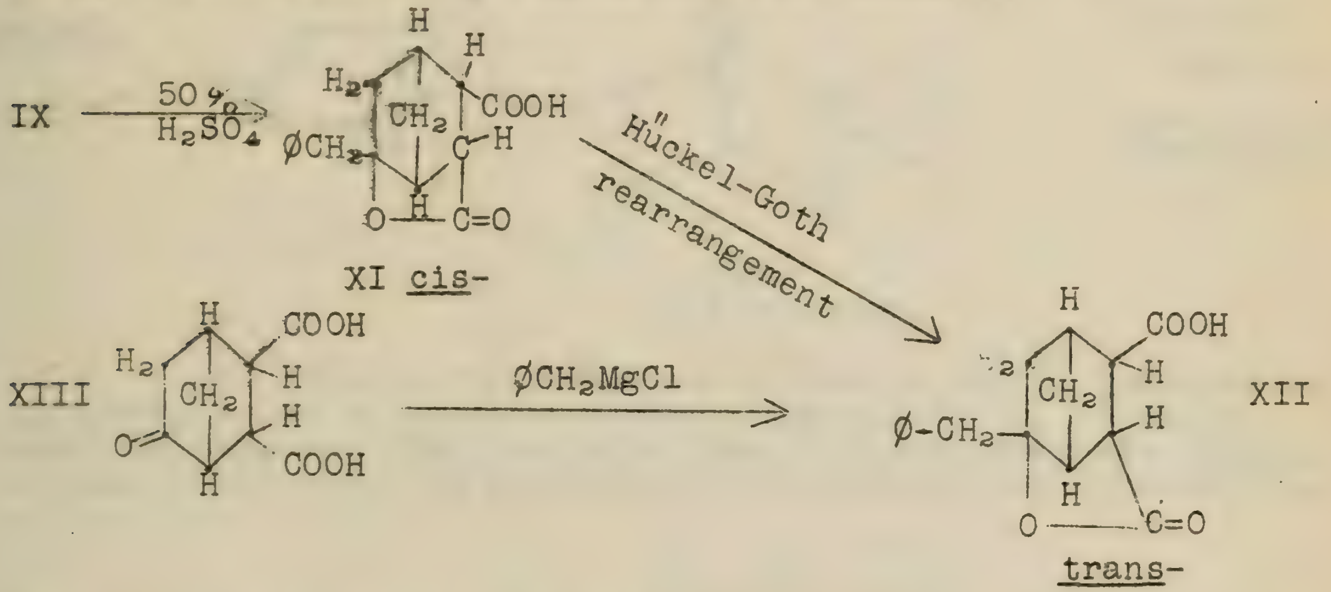
X

from 1-benzyl-

The lower-melting adduct was found to be 4-benzyl-3,6-endomethylene-Δ^4-tetrahydrophthalic anhydride (IX) from the following evidence:

1. $$\text{IX} \xrightarrow[\text{KMnO}_4]{\text{alkaline}} \text{ØCHO}(\longrightarrow \text{ØCOOH}) + \text{cyclopentane-1,2,3,4-tetracarboxylic acid}$$

2. The adduct, upon lactonization and rearrangement of the carboxyl group from cis- to trans- , gave a trans-lactone (XII) identical with that obtained from known trans-3,6-endomethylene-4-keto-hexahydrophthalic acid (XIII).



This fixes the 4-position in the adduct and hence the 2-position in the original benzylcyclopentadiene.

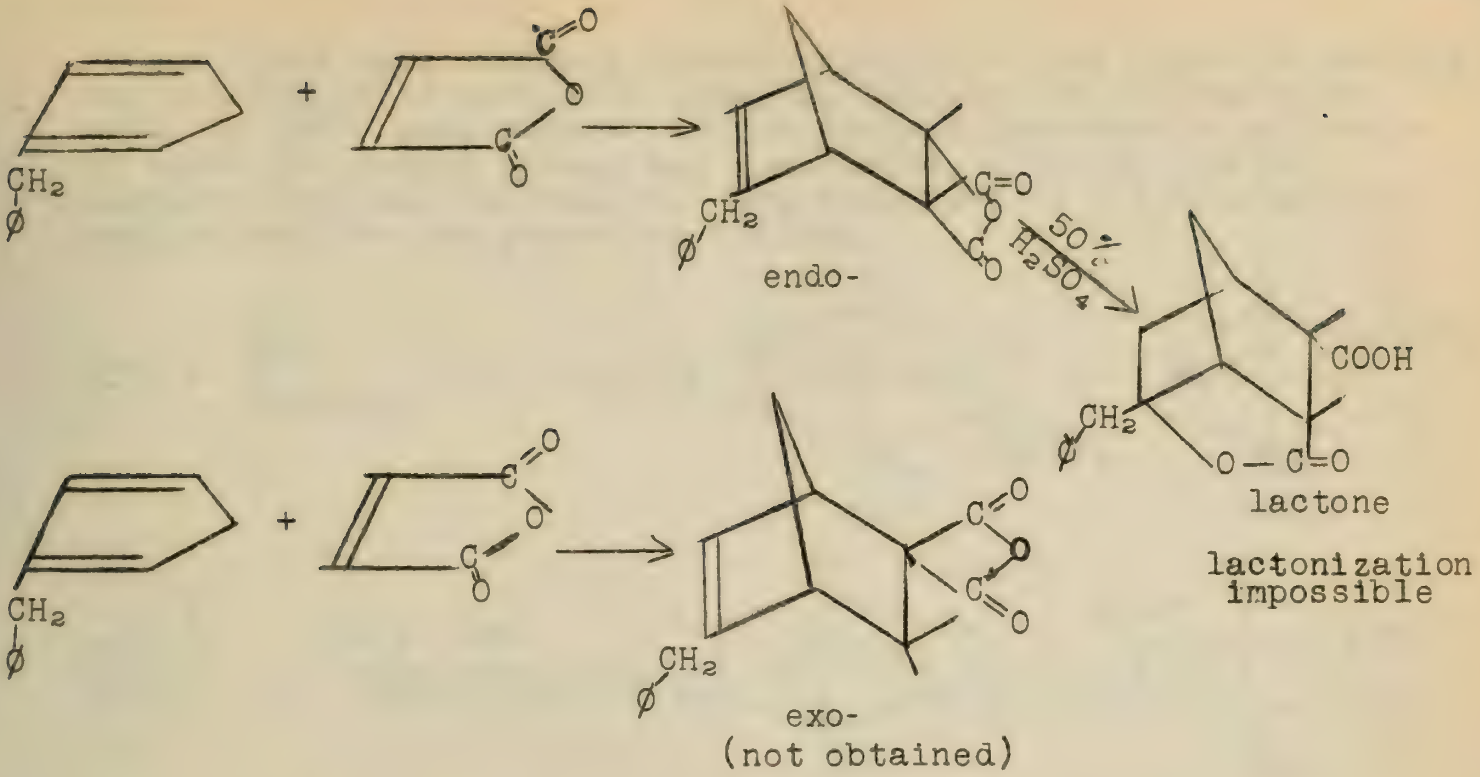
The higher-melting adduct was found to be 3-benzyl-3,6-endomethylene-Δ^4-tetrahydrophthalic anhydride (X):

1. It gave two different (isomeric) mono methyl esters. Of the three remaining possibilities, only X could do this, since VIIIa and VIIIb have planes of symmetry and therefore equivalent carboxyl groups.

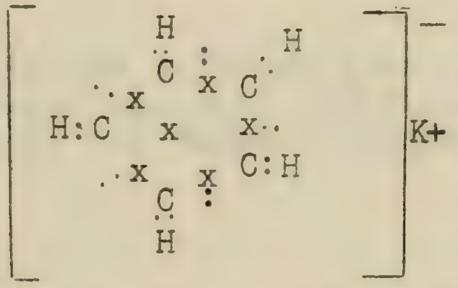
2. Oxidation gave a new tetracarboxylic acid, thought to be 1-benzyl-cyclopentadiene-1,2,3,4-tetracarboxylic acid.

Hence the second mono alkylcyclopentadiene was proved to be the 1-benzyl-derivative.

It is known that Diels-Alder reactions involving cyclopentadiene proceed in a sterically selective fashion; i.e. only the endo-configuration and none of the exo- is obtained. This was shown to be true in the case of the benzylcyclopentadienes by a usual method - that of lactonization of the adduct:

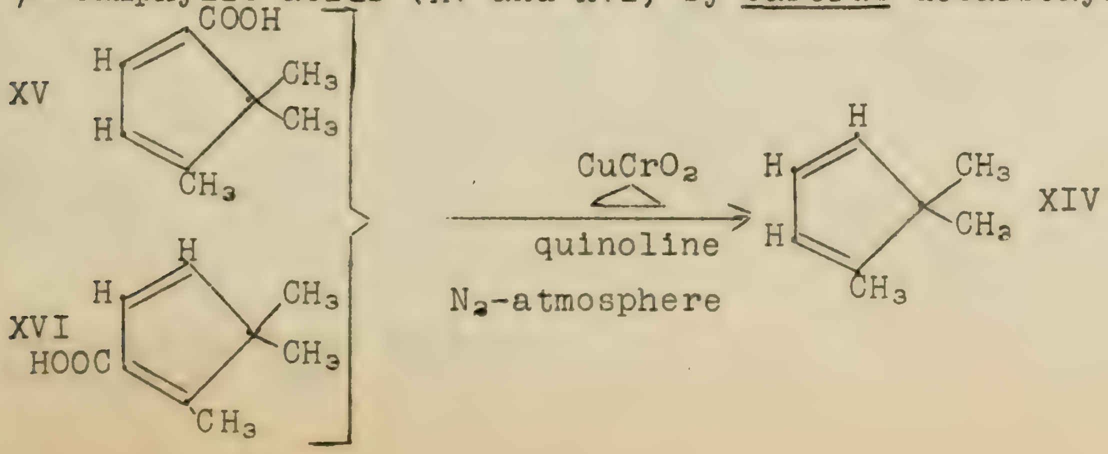


To explain the formation of the 1- and 2- derivatives upon alkylation of cyclopentadiene, instead of the 5- which would be expected upon the principle of least structure change, a symmetrical anion is postulated for potassium cyclopentadiene:

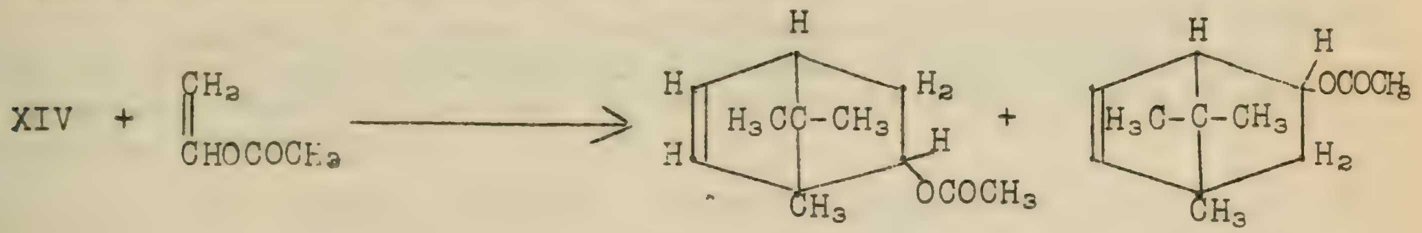


No conclusion is reached as to whether the alkylcyclopentadienes themselves may be adjudged as tautomers on this basis.

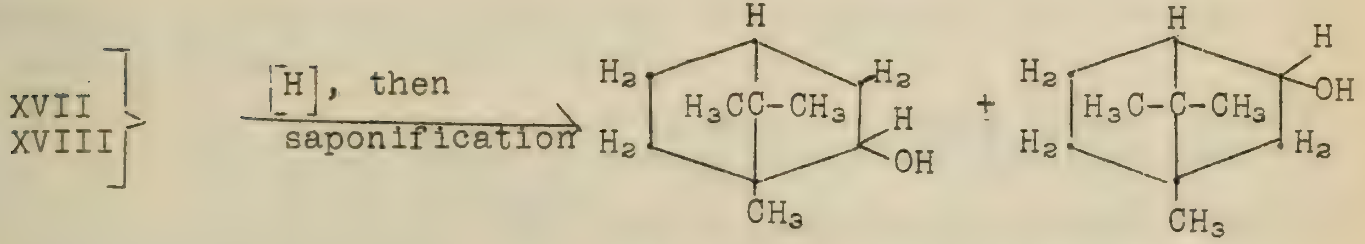
In connection with syntheses in the camphor series, Alder recently found it desirable to prepare 1,5,5-trimethylcyclopentadiene (XIV). In view of the above work, it was unlikely that continued methylation of cyclopentadiene would yield the desired hydrocarbon. It was therefore prepared from α- and β-camphylic acids (XV and XVI) by careful decarboxylation:



It was found that ordinary decarboxylation of the acids by heating the calcium salts with soda lime, as carried out by Damsky as early as 1887, gave instead of the desired hydrocarbon an isomer in which the methyl groups had rearranged, although the 5-membered ring was maintained. The structure of 1,5,5-trimethylcyclopentadiene was proved as follows:



XVII XVIII



dl-borneol dl-epiborneol

When Damsky's hydrocarbon was subjected to the same treatment, neither borneol nor epiborneol was obtained, but instead a new isomeric alcohol.

By reactions similar to those above, 1,5,5-trimethylcyclopentadiene should prove valuable for future syntheses and structure determinations in the camphor series.

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Reported by P. B. Welldon
October 23, 1940

A REVIEW OF SOME OF THE REACTIONS OF ALDEHYDES WITH AROMATIC AMINES

M.A.Sprung - General Electric Co., Schenectady, N. Y.

Reactions between aldehydes and amines ordinarily involve, as the first step, addition of the amine to the carbonyl group of the aldehyde in the same sense as in the first phase of the aldol condensation.

$$RCHO + R'NH_2 \longrightarrow \underset{\displaystyle OH}{\underset{|}{RCH}}\text{-}NHR'$$

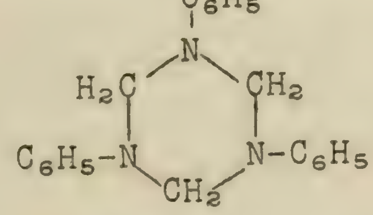
Usually this α-hydroxyamine cannot be isolated, but reacts further in one of several ways:

(1) It may lose water to give the imine (Schiff Base).
(2) It may react further either with itself or with one of the reagents.
(3) The Schiff Base may be involved in various subsequent reactions.

The type of reaction which follows will be determined by the nature of the aldehyde and the amine even more than by the experimental conditions.

I. Reactions of Aliphatic Aldehydes with Aromatic Amines

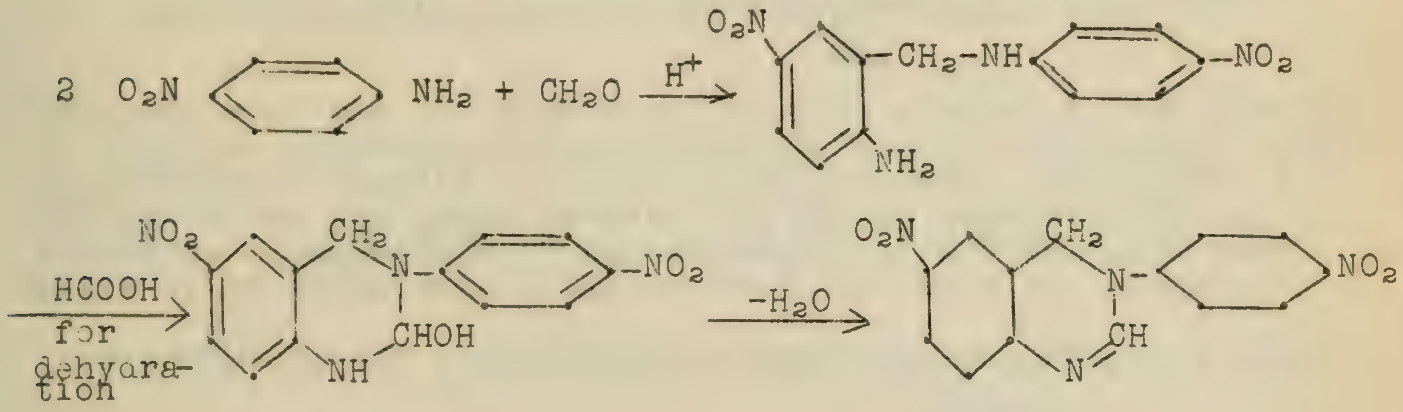
The reactions of formaldehyde with amines differ from those of the other aldehydes due to the greater reactivity of formaldehyde. The most familiar reaction of formaldehyde is that with aniline, which takes place in acid solution under such conditions that the technically useful aniline-formaldehyde resins are obtained. However, when aniline is treated with formaldehyde in dilute, neutral aqueous solution, a compound is obtained which is generally recognized to be a trimer of the hypothetical Schiff base methyleneaniline, $C_6H_5N=CH_2$, and which has the stable six-membered ring structure of triphenyl-trimethylenetriamine.



Apparently this compound is capable of dissociating at higher temperatures and shows a molecular weight in camphor which is only about twice that of the monomer.

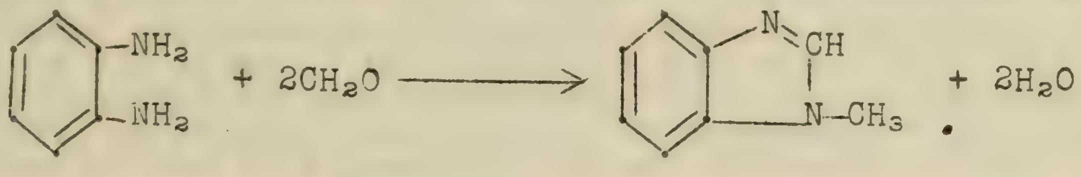
Neither the initial "aldol" nor the Schiff base has ever been isolated, but there is evidence that in alkaline solution one or the other must have a transitory existence.

With the toluidines, nitroanilines, anisidines, phenetidines, and aminobenzoic acids the reactions which occur in neutral or basic solution are analogous to those written for aniline. However, in acid solution, some para-substituted anilines react to give dihydroxyquinazoline derivatives. This is illustrated with p-nitroaniline.



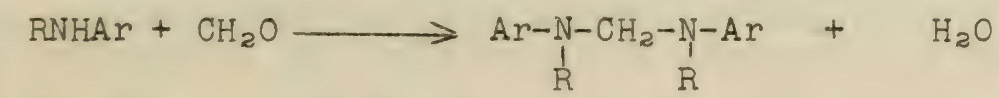
Under more severe conditions polymeric products, similar to the aniline-formaldehyde resins, are obtained.

A somewhat different type of reaction takes place when formaldehyde is mixed with weakly acid solutions of o-phenylenediamine or m-methyl-o-phenylenediamine. The products are N-methylbenzoimidazoles, formed by condensation of two molecules of the aldehyde with one molecule of the diamine.



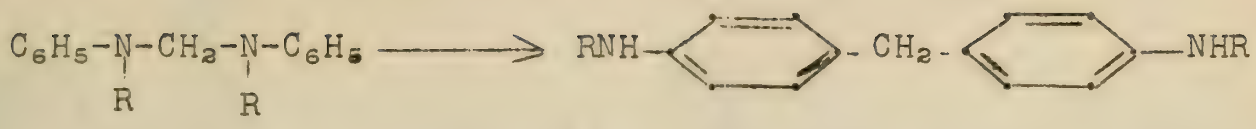
In neutral solution, however, products are obtained which correspond empirically to dimers of the corresponding Schiff bases [bis-(methyleneamino)-benzenes].

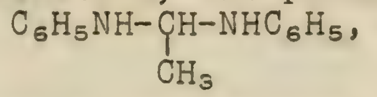
Secondary aromatic amines resinify less readily in the presence of formaldehyde than do the primary amines. Neither do they form the substituted quinazolines. In neutral or slightly alkaline solution the alkyldiphenyl-aminomethanes are readily obtained, according to the equation:



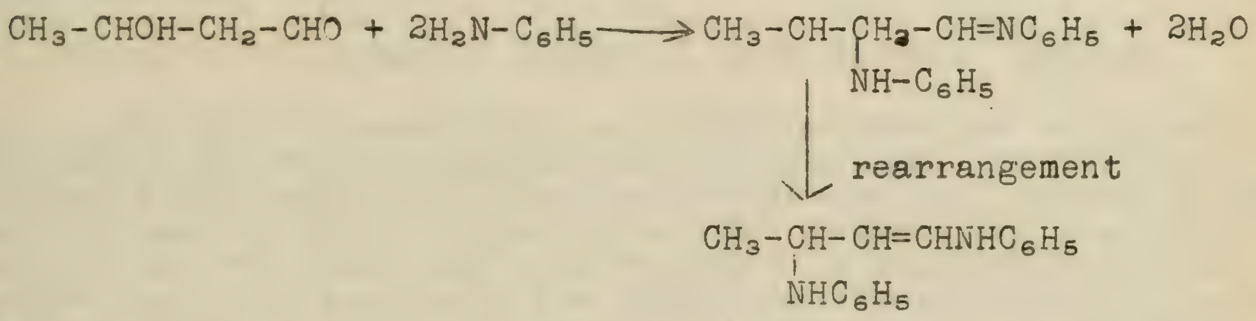
$$RNHAr + CH_2O \longrightarrow \underset{R}{Ar-N}-CH_2-\underset{R}{N-Ar} + H_2O$$

In the presence of hot acid the benzidine type of rearrangement occurs and the p-alkylaminodiphenylmethanes are formed.



The reactions of acetaldehyde with amines are more characteristic of aldehydes in general than those of formaldehyde. If aniline and acetaldehyde are allowed to react in the cold, either in neutral or alkaline solution, the product obtained is 1,1—*bis*-(phenylamino)-ethane,  $C_6H_5NH-\underset{\displaystyle CH_3}{CH}-NHC_6H_5$, m.p. 51°C.

When the reaction is carried out in cold alcohol in the presence of HCl, two crystalline substances are found, both dimers of the hypothetical "ethylideneaniline", $C_6H_5N=CHCH_3$. The dimers are assumed to be *cis*-*trans* isomers and may be conceived of as formed by condensation of two molecules of aniline with one molecule of acetaldol, followed by a 1,3 shift of hydrogen.

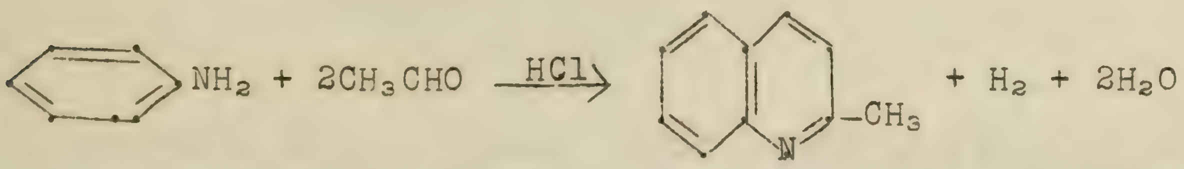


$$CH_3-CHOH-CH_2-CHO + 2H_2N-C_6H_5 \longrightarrow CH_3-CH-\underset{\displaystyle NH-C_6H_5}{CH_2}-CH=NC_6H_5 + 2H_2O$$

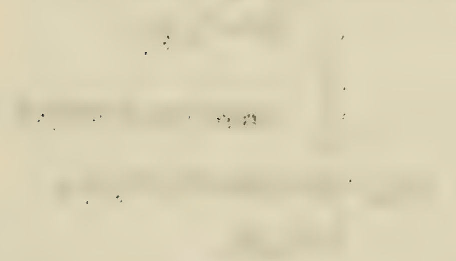
$$\Big\downarrow \text{ rearrangement}$$

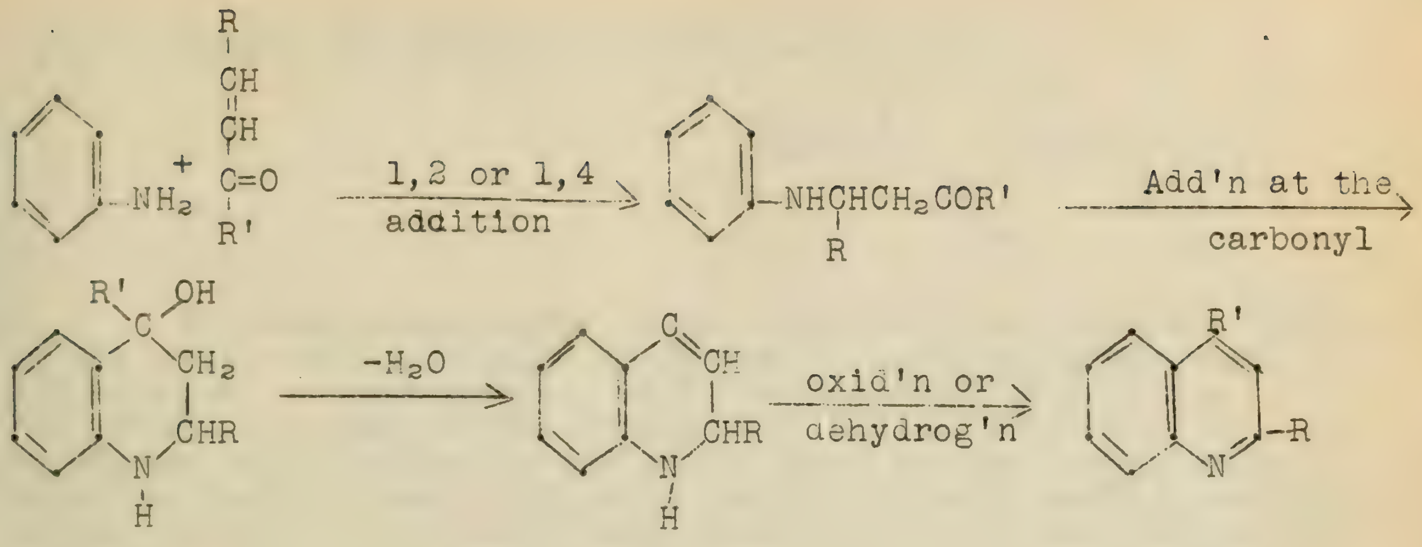
$$CH_3-\underset{\displaystyle NHC_6H_5}{CH}-CH=CHNHC_6H_5$$

When aromatic amines are heated with aliphatic aldehydes in the presence of concentrated hydrochloric acid, a reaction occurs which bears considerable resemblance both to the Skraup quinoline synthesis and to the Tschitschibabin reaction. Ring closure is effected, oxidation and dehydration occur, and a quinoline derivative is formed. In the case of paraldehyde and aniline, the reaction may be represented by the following scheme:



The product, α-methylquinoline, or quinaldine, can also be formed from aniline and aldol. The toluidines and several other substituted anilines react similarly. An investigation of the reaction has indicated that the general mechanism for this quinaldine reaction may best be represented as follows:



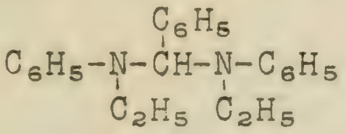


The higher aldehydes tend to give more stable intermediates than does acetaldehyde, but in general the reactions are of the same type.

II. Reactions of Aromatic Aldehydes with Aromatic Amines.

The Schiff bases obtained from the reaction of aromatic aldehydes with aromatic amines are well-defined, crystalline substances and generally do not react further with either of the reagents used in their preparation. The products of the "aldol" stage of the reaction have been arrested in relatively few instances when both reactants are aromatic. Those isolated include the α-amino alcohol from *m*-aminobenzoic acid and benzaldehyde, *m*-$HOOC-C_6H_4-NH-CHOH-C_6H_5$; that from *p*-nitroaniline and benzaldehyde *p*-$NO_2-C_6H_4-NH-CHOH-C_6H_5$; and that from 2,4,6-trinitrobenzaldehyde and aniline, $(NO_2)_3C_6H_2-CHOH-NH-C_6H_5$.

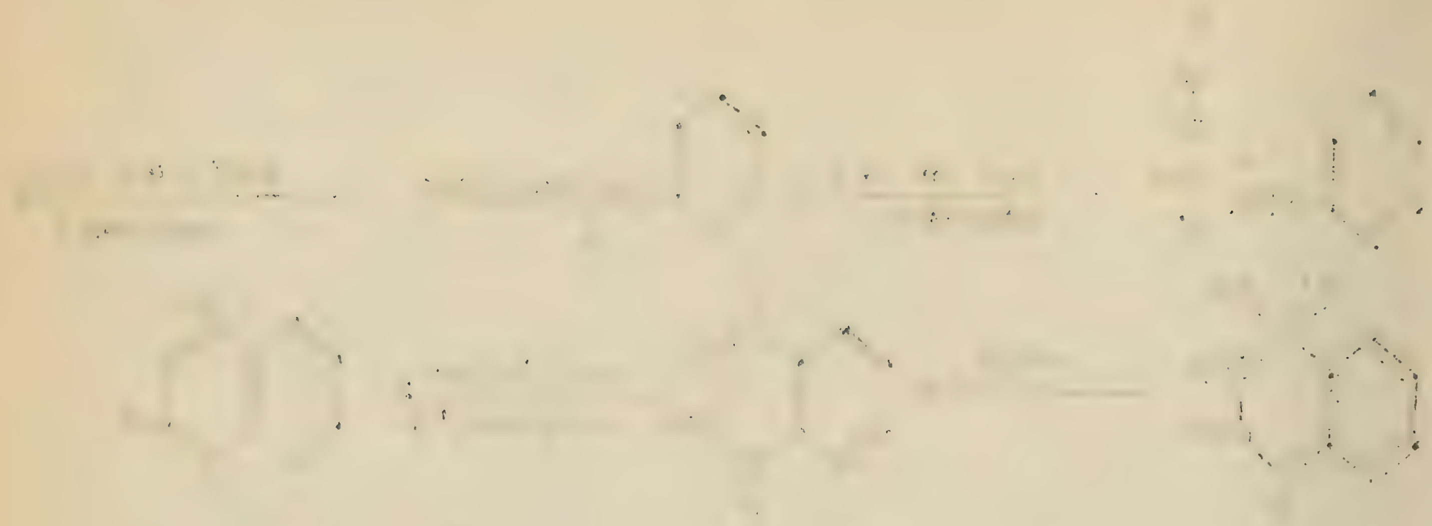
In 1864 Schiff described the reaction product of N-ethylaniline and benzaldehyde to which he ascribed the structure,



$$C_6H_5-\underset{C_2H_5}{N}-\overset{C_6H_5}{CH}-\underset{C_2H_5}{N}-C_6H_5$$

and described it as a "resin" which showed no definite melting point. The reaction product of N-methylaniline and benzaldehyde has not been described in the literature.

Recently, (1938), Veer has shown that disecondary aromatic-aliphatic amines derived from propane can readily be converted to 1,3-diarylhexahydropyrimidines by treatment with the appropriate aromatic aldehyde in aqueous or alcoholic solution. As an example, 1,2,3-triphenylhexahydropyrimidine is thus formed from 1,3-*bis*-(phenylamino)-propane and benzaldehyde.



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II. [illegible]

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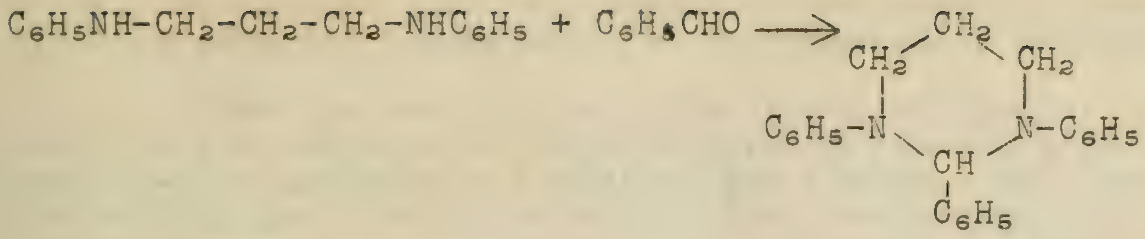
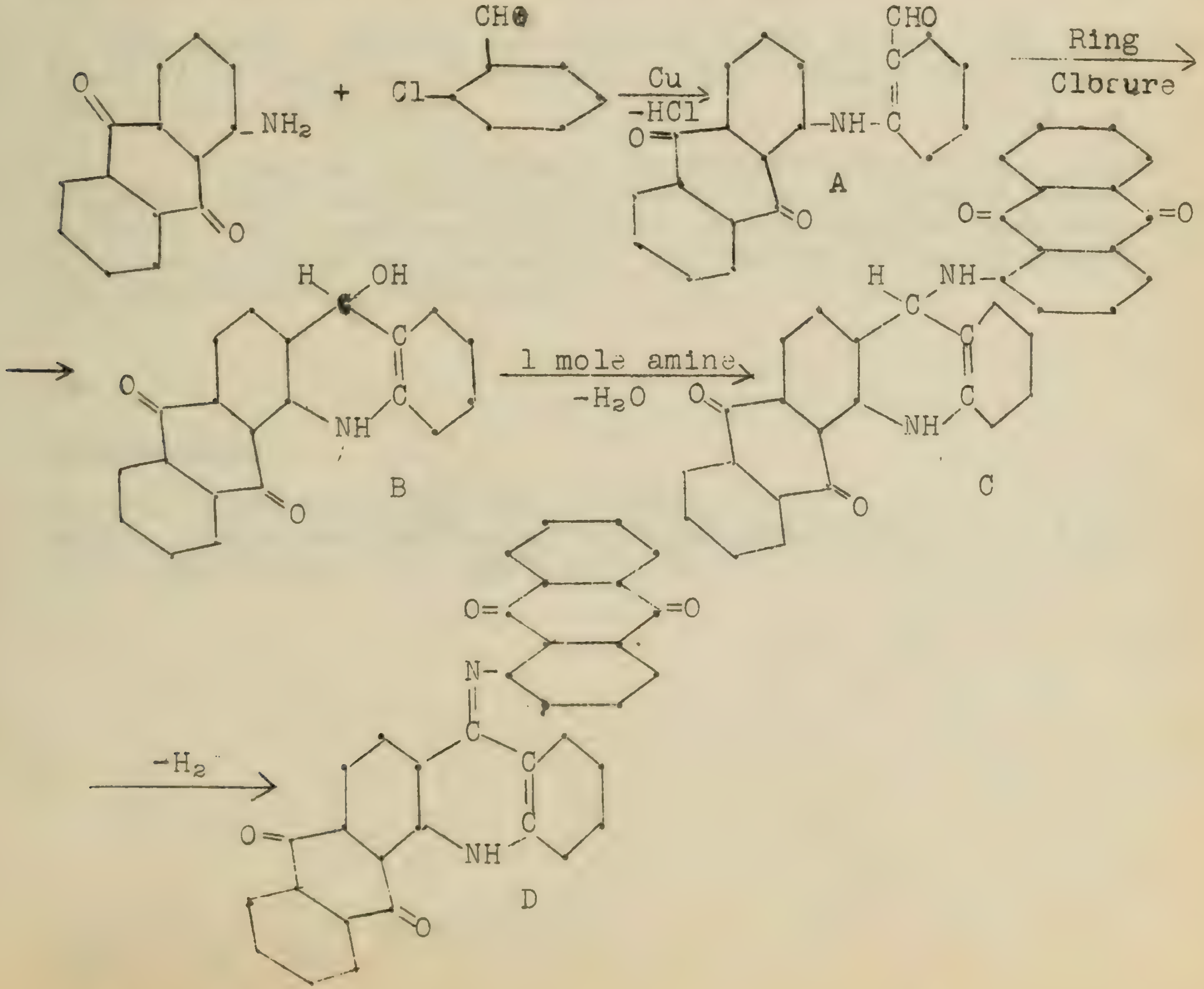
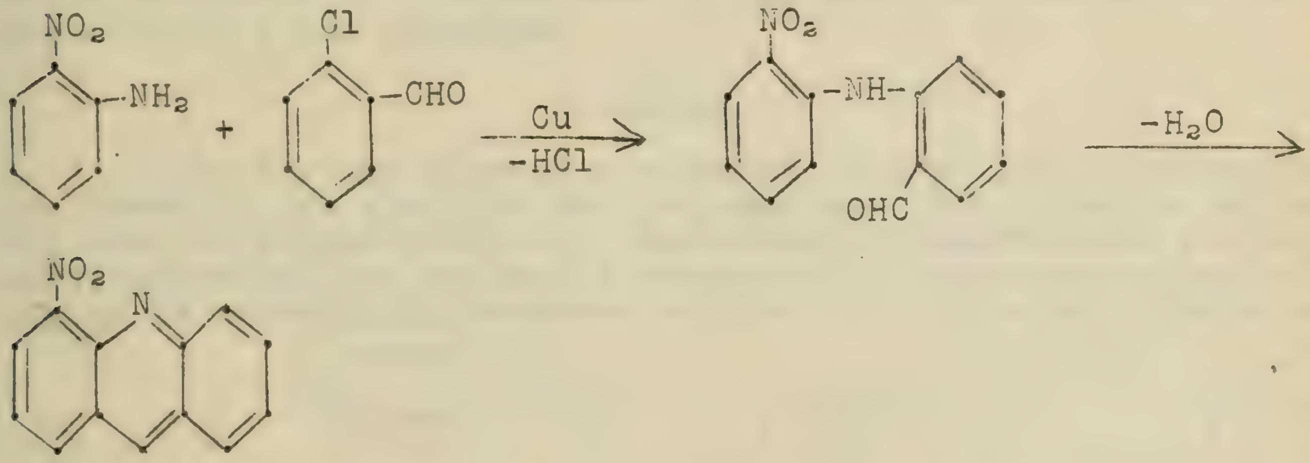


o-Chlorobenzaldehyde forms numerous Schiff bases. However, if the amine is heated with an excess of *o*-chlorobenzaldehyde in nitrobenzene or naphthalene, with the addition of a little "Naturkupfer C" and in the presence of sodium carbonate, an anomalous condensation occurs which leads to the formation of acridine derivatives. This condensation is more easily realized in the case of very weakly basic amines, such as the aminoanthraquinones. The first phase of the reaction is a condensation of the Ullmann type, which leaves the aldehyde group intact. The second phase involves another molecule of amine, and effects ring-closure and concomitant oxidation. This may be illustrated, using 1-amino-anthraquinone as an example. The postulated steps in the acridone synthesis may be outlined as follows:



It will be noticed that this acridone condensation bears a striking external resemblance to the quinaldine reaction.

Under the conditions of the above synthesis, the nitramines react in a somewhat more straightforward fashion with o-chlorobenzaldehyde and simple acridines are formed. This may be illustrated with o-nitroaniline which gives 4-nitroacridine under these conditions.



In many cases, however, the reaction fails to give either acridines or derivatives of acridone. The ordinary Schiff base is then usually obtained.

It may be noted finally that almost any of the amine-aldehyde reactions leads to the formation of tarry or resinous products under certain conditions. The properties and structures of these products will depend on the nature of the reactants and the experimental conditions.

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Reported by L. J. Armstrong
October 30, 1940

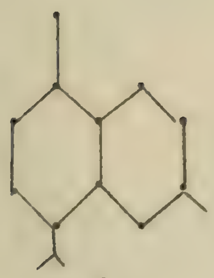
DEHYDROGENATION

R. P. Linstead - University of Sheffield

The principal dehydrogenating agents which have been employed in the examination of compounds of complex hydroaromatic structure have been sulfur, selenium, and the catalytic metals. Although this report is primarily concerned with the latter, it seems advisable to include some of the results obtained by the use of sulfur and selenium.

A. Sulfur

The further removed a compound is from the aromatic state, the lower is the yield on dehydrogenation. Substituents may vary the ease of dehydrogenation. Thus, dihydronaphthalenes are easily dehydrogenated, but the fully hydrogenated tetrahydrocadinene (I) yields no aromatic hydrocarbon with sulfur. Similarly Weiss and Wordich found that 1-(1' naphthyl) cyclohexene (II) gave the corresponding 1-phenylnaphthalene readily with sulfur.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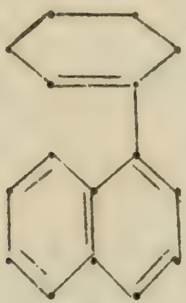
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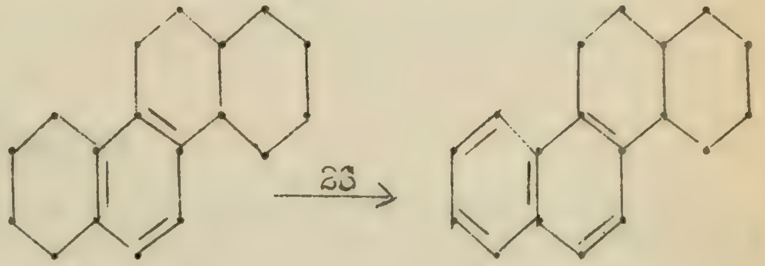
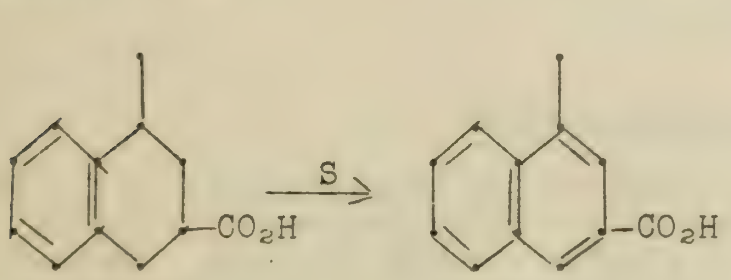


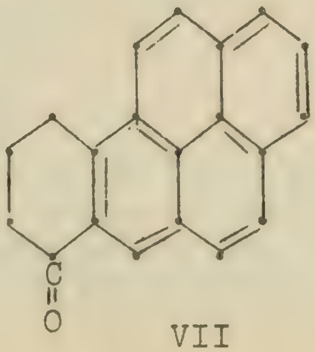
III IV

Less than the theoretical quantity of sulfur will result in only partial conversion to the aromatic state as indicated in the transformation of the dodecahydrochrysene (III) into octahydrochrysene (IV).

Recently the principal applications of sulfur in dehydrogenation have been to oxygenated compounds. Thus, the acid V on treatment with sulfur yielded successfully 1-methyl-3-naphthoic acid (VI).



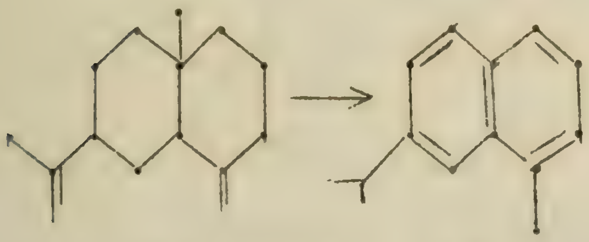
V VI



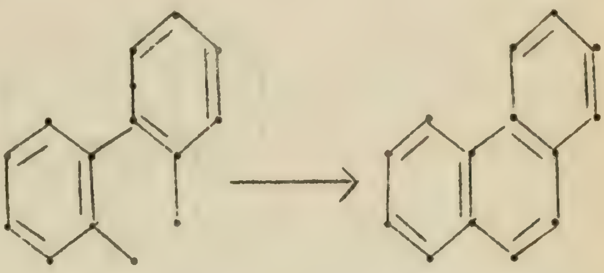
VII

The dehydrogenation of a ketone without secondary decomposition is more difficult than of acids. However, Fieser obtained pure hydroxybenzpyrene by the action of sulfur on ketone VII.

The action of sulfur may result in breaking a carbon-to-carbon bond as in the case of the formation of endolene (IX) from selinene (VIII) in which one carbon is removed; or, conversely, in the formation of a bond as in the case of the transformation of ditolyl (X) into phenanthrene (XI).



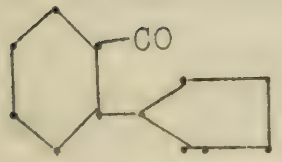
VIII IX



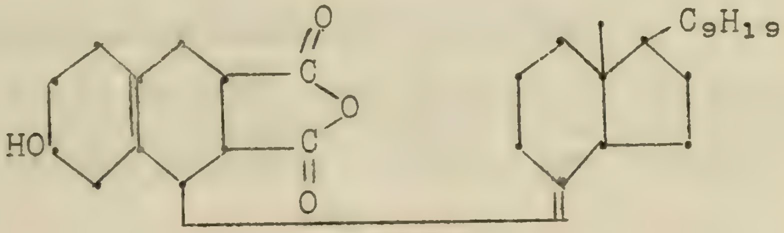
X XI

B. Selenium

There is a general resemblance between the behavior of selenium and sulfur, but normally selenium gives better yields and fewer side reactions. However, two rather exceptionally interesting observations in the literature should be mentioned - namely, the rearrangement of the spiro-ketone (XII) to naphthalene on treatment with selenium, and the conversion of dihydro-derivative of the maleic anhydride adduct of vitamin D_2 (XIII) to the 2,3-dimethylnaphthalene.



XII



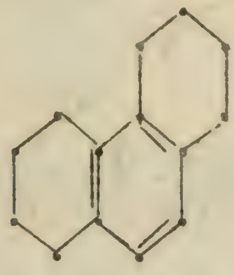
XIII

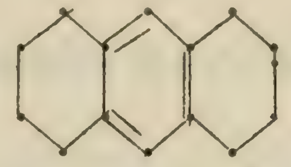
C. Catalytic Metals

Dehydrogenation over noble metals provides a useful auxiliary or alternative method to dehydrogenation by selenium or sulfur. Linstead and co-workers in investigating the conversion of hydroaromatic hydrocarbons into their aromatic counterparts have examined the following substances over such catalysts in the liquid and vapor phases.

1. Substances containing no angular methyl group.

Tetralin. When tetralin was boiled with Pt or Pd, naphthalene was readily formed by direct dehydrogenation without disproportionation of hydrogen. Polycyclic substances containing the tetralin system are dehydrogenated with similar ease as indicated by the quantitative conversion of sulfur octahydrophenanthrene (XIV) and sulfur octohydroanthracene (XV) into the corresponding phenanthrene and anthracene.


XIV


XV

Decalins. Both *cis*- and *trans*-decalins are dehydrogenated by either Pt or Pd in the vapor phase at 300° to naphthalene, but are dehydrogenated very slowly in the liquid phase at the boiling point.

Octalins. When *trans*-Δ^{2}-octalin or $\Delta^{9,10}$-octalin was boiled with Pd, the octalin rapidly underwent disproportionation with subsequent reduction according to the following equations:

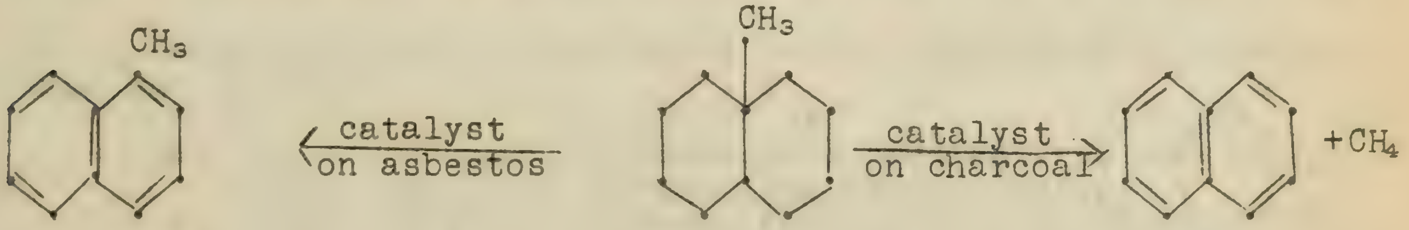
(a) $3C_{10}H_{16} \longrightarrow 2C_{10}H_{18} + C_{10}H_{12}$

(b) $C_{10}H_{12} \longrightarrow C_{10}H_{8} + 2H_{2}$

The relative tendencies for disproportionation and direct dehydrogenation will be bound up in the case of reduction of the double bond in the octalin - the more easily the reduction, the greater the disproportionation.

2. Substances containing an angular methyl group.

In the vapor phase at 300°, the catalytic dehydrogenation of substances containing a quaternary carbon atom can be affected without difficulty, but the reaction can take two courses. Thus -



The migration is of minor importance in the case of compounds in which the quaternary atom carries a *gem*-dimethyl group. Hence, ionene (XVI) when passed over platinized asbestos and

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(a) [illegible]

(b) [illegible]

[illegible]

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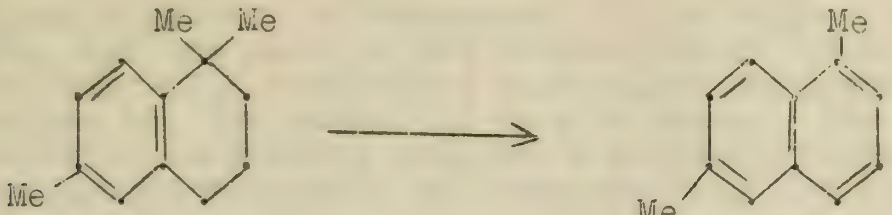
palladized charcoal at 330° yields the 1;6-dimethylnaphthalene (XVII) without the formation of any trimethylnaphthalene.



XVI XVII

3. Formation of Naphthols from alcohols and ketones of the hydronaphthalene group.

A study of the catalytic dehydrogenation in the liquid phase of alcohols and ketones of the hydronaphthalene series, both tetrahydro- and dehydro-type and containing the oxygen atom in the α or β position, is summarized in Table I. The catalyst most generally used is palladized charcoal in dilute solution.

Table I

Compound	% Yield of total Aromatic Material	% Yield of Naphthol
α-Tetralone	81	46 α-
ar-β-Tetralol	97	55 β-
ac-β-Tetralol	96	60 β-
trans-α-decalone	97	19 α-
trans-β-decalone	61	41 β-; β,β'-dinaphthyl also
cis-β-decalone	69	28 β-
trans-β-decalol	51	17 β-
cis-β-decalol	56	12 β-

With reference to the above table, the following observations can be made:

a. As the compound becomes more removed from the aromatic type, the yield of phenolic product falls.
b. There is a facilitating influence of an aromatic ring already present.
c. Ketones are more readily dehydrogenated than alcohols.
d. There is an indication that *cis*-compounds are more readily dehydrogenated than the *trans*.

4. Catalytic disproportionation of some terpenes and terpene ketones.

A study has been made of the action of palladium and platinum catalysts on compounds of the terpene and sesquiterpene series, and the results are summarized in Table II. The experiments under mild conditions gave clear evidence of the skeleton structure and the number of double bonds. For instance, all the unsaturated substances underwent disproportionation into aromatic and saturated compounds at comparatively low temperatures (140°-205°), the proportions found being predictable from the number of double bonds.

Table II

Terpene	Optimum Conversion to Aromatic Counterpart
Limonene	80% p-cymene - vapor phase dehydrogenation at 350°
Pinene	75% p-cymene - vapor phase dehydrogenation at 300°
Cadinene	50%-Cadalene - Liquid phase disproportionation at 243°
Selinene	37%-Eudalene - Liquid phase disproportionation at 205°
Pulegone	59% Thymol - Vapor phase dehydrogenation at 300°
Carvone	95% Carvacrol - Liquid phase rearrangement at 220°
Dehydrocarvone	80% Carvacrol - Liquid phase dehydrogenation at 225°
Menthone	84% Thymol - Liquid phase dehydrogenation at 204°

Disproportionation

Terpene	Temp.	Products	Proportions Found	Proportions Calc.
Limone	140°	p-cymene + p-menthane	2:0:9	2:1
Pinene	156°	p-cymene + pinane	1:1:1	1:1
Cadinene	186°	Cadalene + tetrahydrocadinene	2:2.6	2:3
Selinene	205°	Eudalene + tetrahydroselinene	2:2:9	2:3
Pulegone	175°	Thymol + menthone	1:0.9	1:1

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Reported by J. M. Wilkinson, Jr.
October 30, 1940

THE MERCURATION OF ETHYLENIC COMPOUNDS

Hofmannand Sand found that ethylene and mercuric or basic mecuric salts react, in aqueous solution, to form compounds which they considered to have the structures,

$$HO-CH_2CH_2-HgX \quad \text{and} \quad XHg-CH_2CH_2-O-CH_2CH_2-HgX$$

since they will react with iodine to form ethylene iodohydrin and diiodoethyl ether. In alcohol solution a single substance was obtained, the structure of which was represented as $R-O-CH_2CH_2-HgX$.

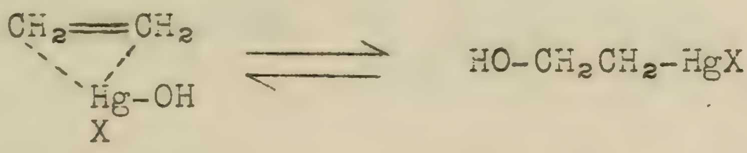
However, these salts are very unstable to acids forming mercuric salt, ethylene and water or alcohol:

$$HO-CH_2CH_2-HgX + HX \longrightarrow HgX_2 + H_2O + C_2H_4$$

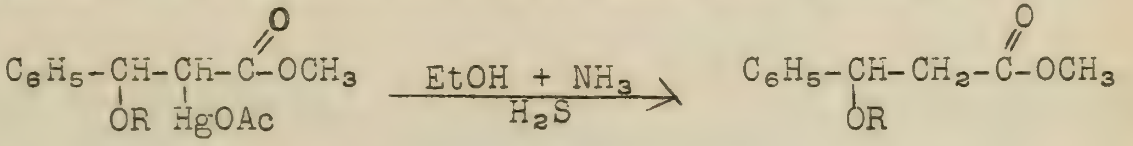
If we had an ordinary RHgX compound we would have expected it to form RH:

$$RHgX + HX \longrightarrow RH + HgX_2$$

Sand therefore modified his views and considered the compound to be tautomeric:



Manchot prefers to formulate these substances merely as double salt or molecular compounds; such as $C_2H_4Hg(OH)X$. However, transformations of the following type have been observed:

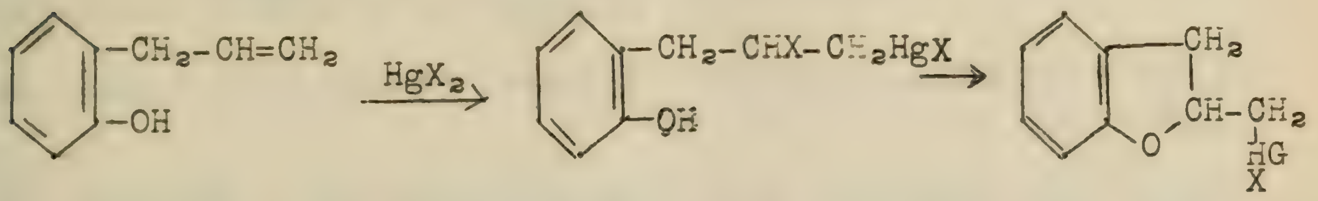


$$C_6H_5-\underset{OR}{CH}-\underset{HgOAc}{CH}-\overset{O}{\overset{/\!/}{C}}-OCH_3 \xrightarrow[H_2S]{EtOH + NH_3} C_6H_5-\underset{OR}{CH}-CH_2-\overset{O}{\overset{/\!/}{C}}-OCH_3$$

It should be noted that in this, as well as in similar cases, the reagents used will not convert the original ethylenic compound into the final product, and therefore it would be unlikely that we have a double salt. Similarly it would be difficult to explain the reduction of $HOCH_2CH_2HgX$ and of $CH_3CHOHCH_2HgX$ to ethyl and isopropyl alcohols, if we were to assume molecular compounds.

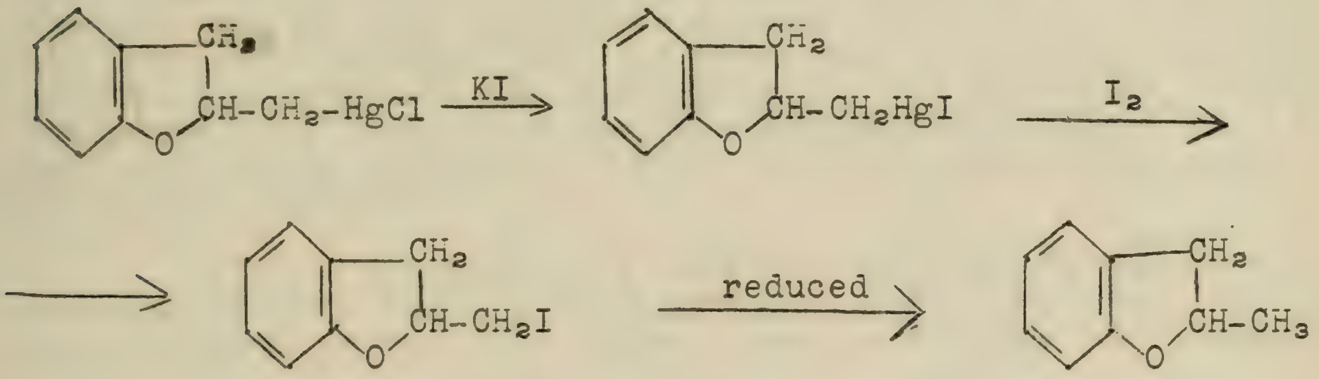
Another argument against the double salt formulation is the fact that a number of cases have been observed where the mercury salt adducts are stable to acid. For example, the dibenzoyl derivative of $HOCH_2-CHOH-CH_2HgX$ is stable to concentrated hydrochloric acid.

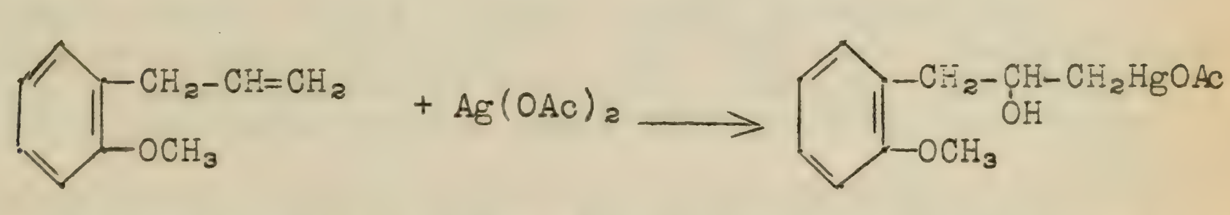
To gain insight into the structure of these compounds, Adams treated o-allyl phenol with mercuric salts to obtain mercurated dihydrobenzofurans.



This reaction works similarly in water or alcohol solution, and therefore the above must be the correct mechanism. The product is stable to acid and hence a good yield may be obtained in the absence of alkali. Ordinarily the normal mercuric salts add to the double bond, but the acid group directly attached to carbon hydrolyzes to produce acid which reverses the addition.

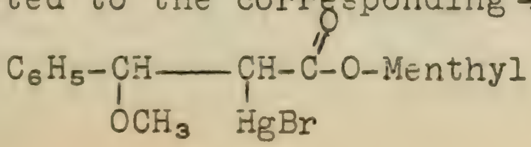
The dihydrobenzofurans were produced in practically quantitative yields. The structure of the product was proven by the following method:





This reaction will not go with $HgCl_2$, since the product is unstable to acids.

Marvel demonstrated that the mercury salt adducts must be represented by the ordinary formulas representing addition to the double bond, by showing that new assymmetric centers may be formed in the reaction. He prepared the methoxymercurial from l-menthyl cinnamate with mercuric acetate in methanol. He was unable to separate the diastereoisomers, but when the compound was converted to the corresponding -HgBr or -HgI compound;

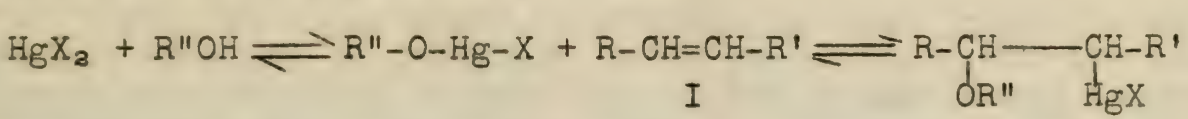


$$C_6H_5-\underset{OCH_3}{CH}-\underset{HgBr}{CH}-\overset{O}{\overset{\|}{C}}-O-\text{Menthyl}$$

there were obtained two of the four theoretically possibly active forms. In the case of d-bornyl β-methoxy-α-bromomercuri hydrocinnamate, it was also possible to isolate two forms.

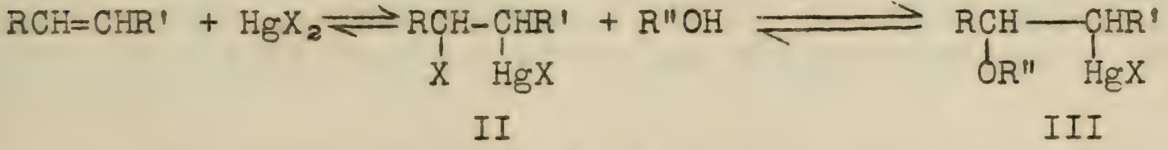
Wright has carried out work designed to show whether mechanism A or B is the correct one:

A.



$$\mathrm{HgX_2 + R''OH \rightleftharpoons R''\text{-}O\text{-}Hg\text{-}X + \underset{I}{R\text{-}CH{=}CH\text{-}R'} \rightleftharpoons \underset{OR''}{R\text{-}CH}\text{---}\underset{HgX}{CH\text{-}R'}}$$

B.



$$\mathrm{RCH{=}CHR' + HgX_2 \rightleftharpoons \underset{II}{\underset{X}{RCH}\text{-}\underset{HgX}{CHR'}} + R''OH \rightleftharpoons \underset{III}{\underset{OR''}{RCH}\text{---}\underset{HgX}{CHR'}}}$$

A kinetic study in the case of methyl cis-cinnamate indicates that the reaction is of the second order. Mechanism B has an obnoxious feature, the formation of an ether III from an ester II.

It might be imagined that the first step of mechanism B might be the rate controlling step, but Hugel and Hibou have found that addition compounds of type II are formed in a few minutes. However, the methoxy-mercurials (except in the case of styrene) do not form this rapidly. Also if the above is true the alcohol should have little effect on the reaction rate, but Schoeller, Schrauth and Struensee have found that the reaction proceeds slowly in water, more rapidly in methanol and that the rate decreases rapidly with the higher alcohols.

It is unlikely that in methanol solution the methoxymercuric acetate adds as methoxy and acetomercury ions. Methyl cis-cinnamate reacts about three times as rapidly as the trans-form.

This indicates that addition occurs by way of the undissociated methoxymercuric acetate since the space configuration should offer little hindrance to the ions. Similarly isostilbene (cis-) gives a good yield whereas trans-stilbene does not react.

Wright has recently investigated the methoxymercurials from cis- and trans-styryl cyanide. He hoped that, since the cis-form reacts more rapidly than the trans-form, this would be a good reaction to use to determine which isomer of a pair is cis- or trans- and, perhaps also, to determine the ratio of cis- to trans- in mixtures.

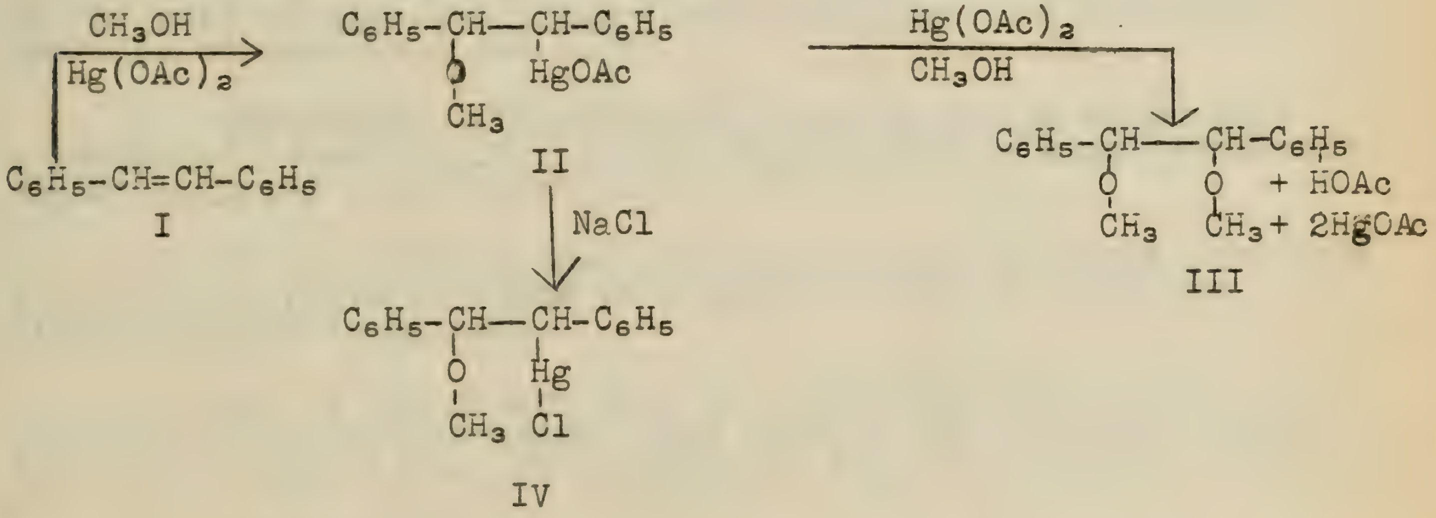
It was found that neither cis- nor trans-styryl cyanide reacted appreciably with a methanol solution of mercuric acetate at room temperature. However, using a small amount of nitric acid as a catalyst is effective in increasing the reactions to measurable values. The analytical procedure involved chloroform extraction to remove the organomercurial and the excess of the original ethylene, the mercuric acetate in the aqueous layer then being titrated with thiocyanate.

At 25° it was found that, using 0.0003 mole of nitric acid per 0.01 mole of mercuric acetate and 0.01 mole of styryl cyanide in methanol, the reaction stopped after 5 hours. At this point the addition of 0.0015 mole of nitric acid caused the reaction to proceed to completion.

In the experiments with both cis- and trans- isomers there was obtained an infusible white precipitate and the mercurial. In the slower reaction in the case of the trans-isomer it was found that there was more precipitate than in the case of the cis-isomer. It contains mercury and nitrogen. It is, therefore, undoubtedly involved in a side reaction involving the destruction of the nitric acid catalyst.

The structure of both of the mercurials was determined by bromination to produce a mixture of the known α-bromo-β-methoxy-β-phenylpropionic acids.

In a more recent article Wright has investigated the catalysis in the production of the α-methoxymercurials. He found that no mercurial could be isolated from the reaction of trans-stilbene with mercuric acetate in methanol, but that mercurous salt was precipitated over a period of days. Wright found that the equivalent quantity of mercuric acetate was reduced in 15 days at 25°. If the solution is then heated with a second mole of mercuric acetate for four days, 1,2-dimethoxy-1,2-diphenylethane was isolated in 20% yield. This compound could also be prepared from 1-chloromercuri-2-methoxy-1,2-diphenylethane from cis-stilbene by the action of mercuric acetate in methanol. It therefore appears that trans-stilbene formed a mercurial, II, but so slowly that it was converted by unchanged mercuric acetate to the dimethoxy compound III.



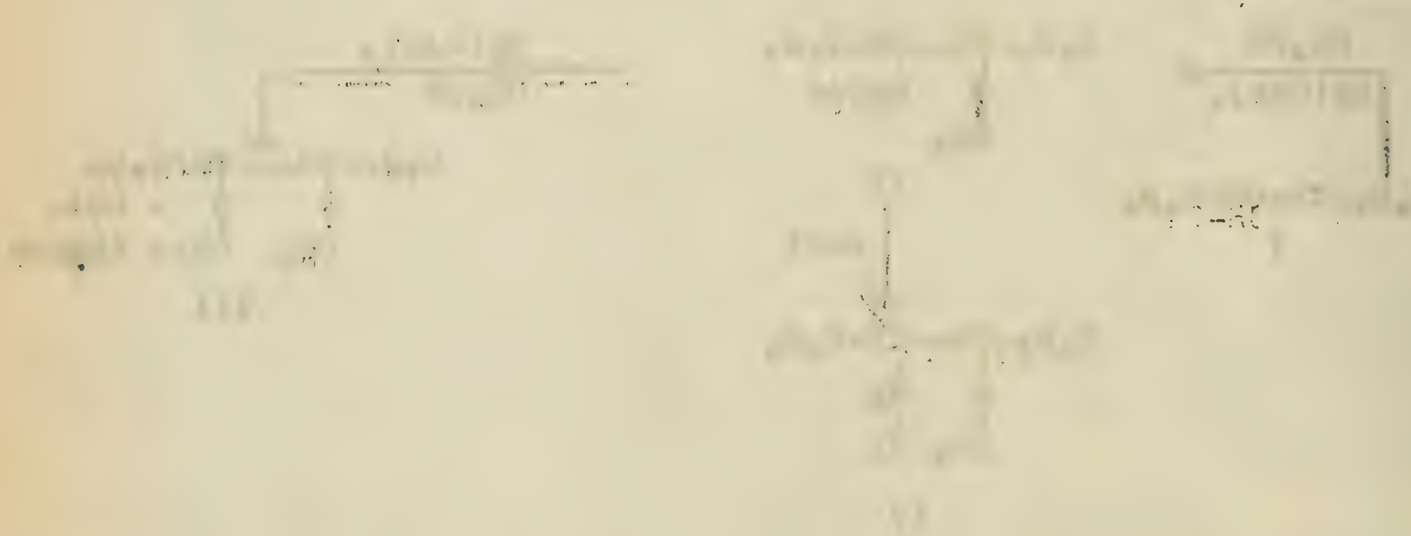
It was found that nitric acid had no effect on this reaction with cis-stilbene. They used instead 0.1 equivalent of peroxide such as benzoyl peroxide or ascaridole. With this catalyst trans-stilbene was converted in one day to a 1-chloromercuri-2-methoxy-1,2-diphenylethane in 24% yield.

[illegible]

[illegible]

[illegible]

[illegible]



IV

[illegible]

It was considered that the effect of nitric acid was related to its peroxide forming ability in methanol. It was similarly found that peroxides initiated reaction between styryl cyanide and mercuric acetate in methanol, but that the catalyst is destroyed so rapidly that the reaction could not be carried to completion.

It was suggested that the cyano group was responsible for the lower reactivity of styryl cyanide than that of the other ethylenes. To test this acetonitrile was added to benzalacetophenone in a methanol solution of mercuric acetate. It was found that the addition of one mole of acetonitrile retarded the rate from a half life of sixty minutes to a half life of one hundred and eighty minutes.

In a similar way the addition of styryl cyanide retarded the above reaction to the same extent.

Pyridine was found to inhibit the reaction to a greater extent. One equivalent almost stopped the reaction.

It was found that diethyl disulfide which might resemble the peroxides retards the addition. The explanation of these retardations is that acetonitrile and pyridine form coordination compounds readily and it was shown that diethyl disulfide forms a salt with the mercuric acetate in methanol. It was a mixed mercuric salt of acetic acid and methyl mercaptan.

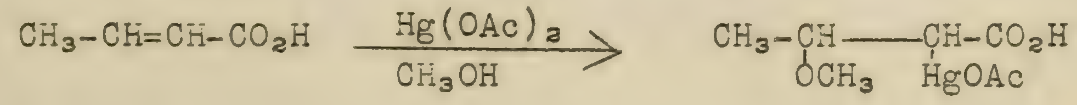
Since peroxides are electron acceptors and pyridine and nitriles are electron donors, it was predicted that boron salts, being acceptors, would accelerate the reaction. It was, indeed, found that boron trifluoride etherate caused marked acceleration in the case of cis- and trans-styryl cyanides, but that the reaction stopped in a few hours.

Mechanism: The mechanism must be one in which each geometrical isomer yields its own characteristic diastereoisomer uncontaminated with the other.

It is unlikely that addition occurs by way of carbonium ions or free radicals since we would then expect to obtain diastereoisomeric mixtures.

One of the recent uses of methoxymercurials is in the preparation of certain amino acids such as threonine and serine. These two preparations are included in Organic Syntheses, Volume 20.

dl-Threonine:



$$CH_3-CH=CH-CO_2H \xrightarrow[CH_3OH]{Hg(OAc)_2} CH_3-\underset{OCH_3}{CH}-\underset{HgOAc}{CH}-CO_2H$$

The subsequent steps involve transforming the above to the HgBr compound with KBr, the treatment of this with Br_2 in KBr solution to replace HgBr with Br, the replacement of the bromine by the amino group with ammonia, the protection of the amino group with formic acid and the hydrolysis of the methoxy group with HBr. This gives dl-threonine hydrobromide which is then treated with NH_3.

dl-Serine: The reaction here is quite similar, involving the use of methyl acrylate in place of the crotonic acid above.

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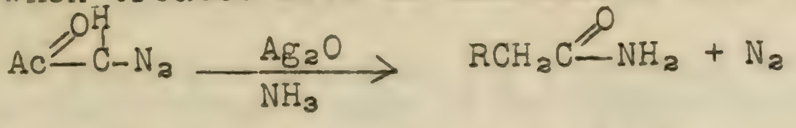
Reported by B. D. Deacon
November 6, 1940

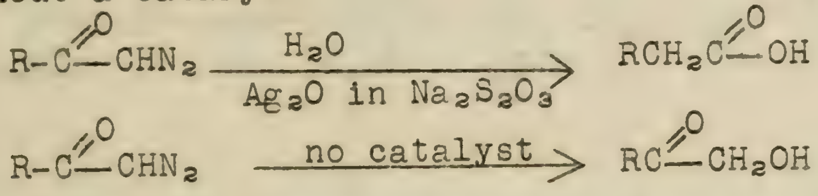
THE ARNDT-EISTERT (WOLFF) REARRANGEMENT

In 1912 Wolff described a rearrangement which diazoketones undergo when treated with an ammoniacal solution of silver oxide.



$$\mathrm{Ac\overset{OH}{=}C{-}N_2 \xrightarrow[NH_3]{Ag_2O} RCH_2\overset{O}{\overset{\|}{C}}{-}NH_2 + N_2}$$

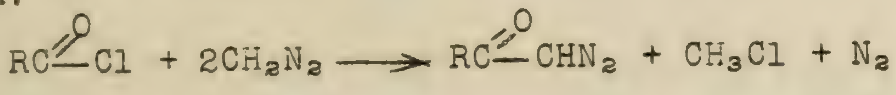
He also described the action of water on diazoketones, both with and without a catalyst.



$$\mathrm{R{-}\overset{O}{\overset{\|}{C}}{-}CHN_2 \xrightarrow[Ag_2O\ in\ Na_2S_2O_3]{H_2O} RCH_2\overset{O}{\overset{\|}{C}}{-}OH}$$

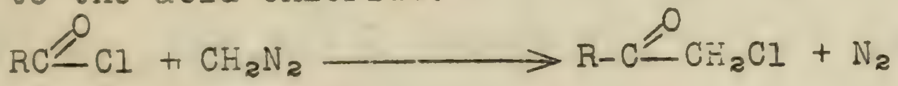
$$\mathrm{R{-}\overset{O}{\overset{\|}{C}}{-}CHN_2 \xrightarrow{no\ catalyst} R\overset{O}{\overset{\|}{C}}{-}CH_2OH}$$

Wolff prepared the diazoketones by the action of nitrous acid on α amino ketones. Since these were difficult to obtain the rearrangement was of little value as a synthetic method. In 1928 Arndt and Amende developed a general method of preparing diazoketones by adding an acid chloride to an excess of diazomethane solution.



$$\mathrm{R\overset{O}{\overset{\|}{C}}{-}Cl + 2CH_2N_2 \longrightarrow R\overset{O}{\overset{\|}{C}}{-}CHN_2 + CH_3Cl + N_2}$$

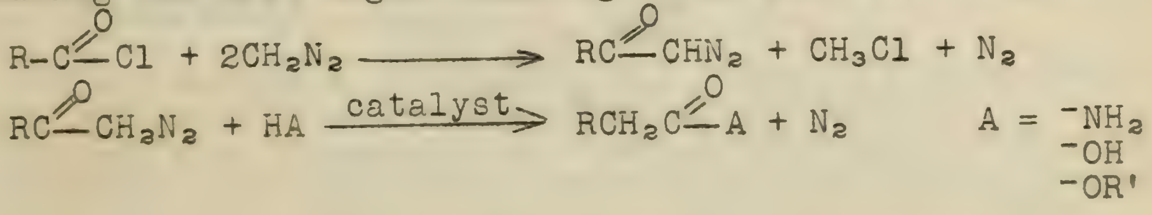
In connection with this it is interesting to note that chloroketones were obtained by Nierenstien and Staudinger by adding the diazomethane to the acid chloride.



$$\mathrm{R\overset{O}{\overset{\|}{C}}{-}Cl + CH_2N_2 \longrightarrow R{-}\overset{O}{\overset{\|}{C}}{-}CH_2Cl + N_2}$$

Arndt and Amende explained these differing results by assuming an intermediate addition compound which loses hydrogen chloride to give the diazoketone. An excess of diazomethane would react with the hydrogen chloride to form methyl chloride and nitrogen, and the diazoketone would be obtained as the chief product. However, in the absence of an excess of diazomethane the hydrogen chloride would decompose the diazoketone to give the chloroketone.

In 1935, Arndt and Eistert showed that the rearrangement of the diazoketone described by Wolff could also be catalyzed by finely divided metals such as showed Ag, Pt, and Cu. They also found that the decomposition of the diazoketones in the presence of an alcohol led to the formation of an ester. A general method for producing the next higher homolog of an acid was obtained.

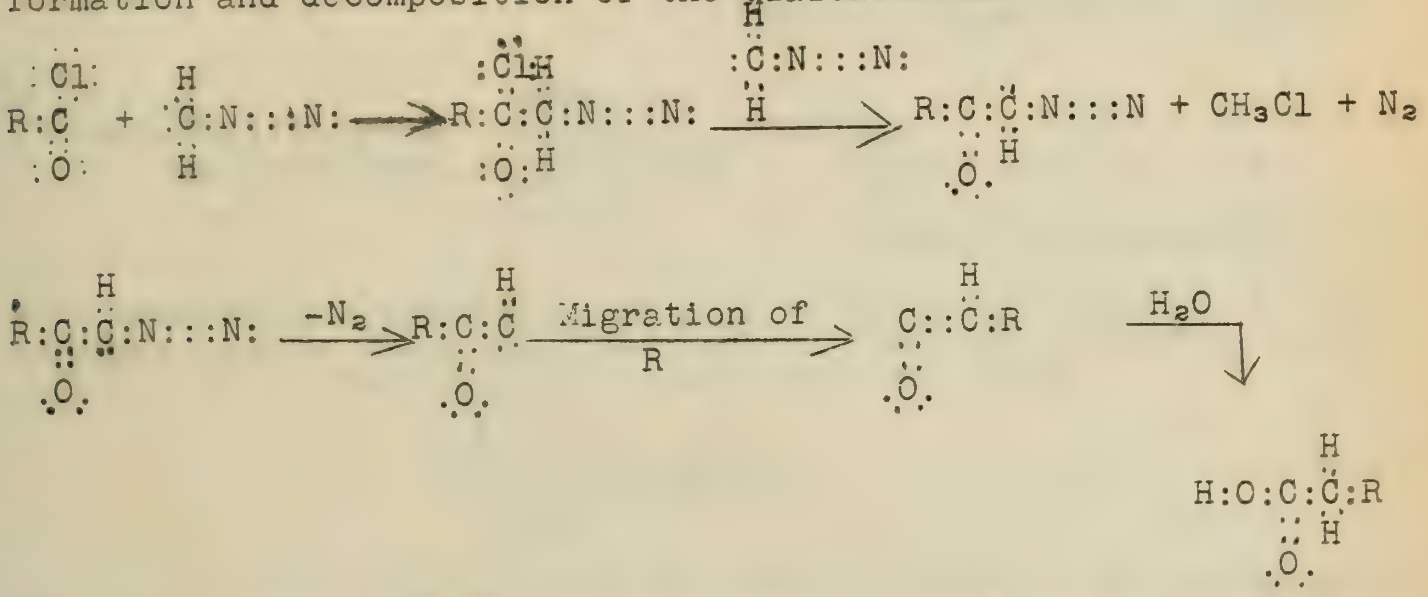


$$\mathrm{R{-}\overset{O}{\overset{\|}{C}}{-}Cl + 2CH_2N_2 \longrightarrow R\overset{O}{\overset{\|}{C}}{-}CHN_2 + CH_3Cl + N_2}$$

$$\mathrm{R\overset{O}{\overset{\|}{C}}{-}CH_2N_2 + HA \xrightarrow{catalyst} RCH_2\overset{O}{\overset{\|}{C}}{-}A + N_2 \qquad A = {^-}NH_2,\ {^-}OH,\ {^-}OR'}$$

The rearrangement to the amide in the presence of ammonia seems to be a more dependable reaction than that which produces the free acid or its ester by the action of water or an alcohol respectively. The best method of preparing the higher homolgous acid is, therefore, in many cases, the preparation of the amide followed by hydrolysis.

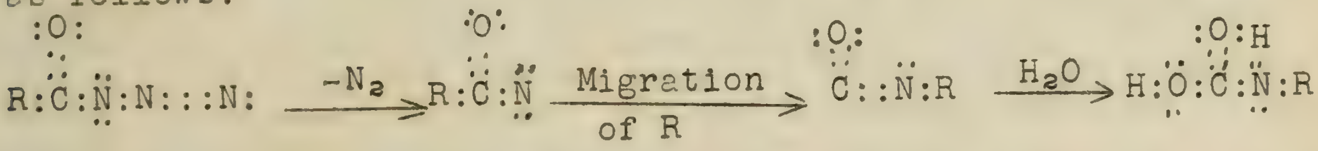
Wistert has proposed the following mechanism for the formation and decomposition of the diazoketones.



$$R{:}C + :C{:}N{:::}N: \longrightarrow R{:}C{:}C{:}N{:::}N: \xrightarrow{H} R{:}C{:}C{:}N{:::}N + CH_3Cl + N_2$$

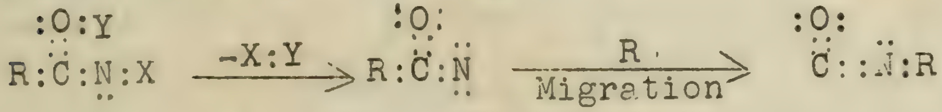
$$R{:}C{:}C{:}N{:::}N: \xrightarrow{-N_2} R{:}C{:}C \xrightarrow[R]{\text{Migration of}} C{::}C{:}R \xrightarrow{H_2O} H{:}O{:}C{:}C{:}R$$

He compared this to the Curtius decomposition which he postulated as follows:



$$R{:}C{:}N{:}N{:::}N: \xrightarrow{-N_2} R{:}C{:}N \xrightarrow[\text{of R}]{\text{Migration}} C{::}N{:}R \xrightarrow{H_2O} H{:}O{:}C{:}N{:}R$$

This agrees with a general mechanism proposed by Jones and Hurd for the Curtius, Lossen, and Hofmann rearrangements.



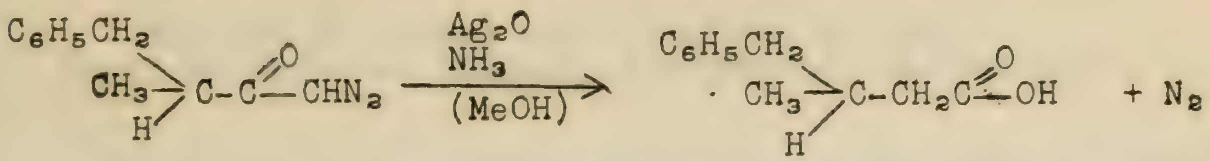
$$R{:}C{:}N{:}X \xrightarrow{-X:Y} R{:}C{:}N \xrightarrow[\text{Migration}]{R} C{::}N{:}R$$

The isocyanate intermediate in these rearrangements can be isolated under proper conditions, and, in the absence of substances having an active hydrogen, the ketone intermediate in the decomposition of a diazoketone may sometimes be isolated. Thus the dimer of the ketone formed in the decomposition of the methyl ester of diazoacetic acid was obtained by Staudinger and Hirzel and also by Schroeter.

Wallis and his coworkers had previously shown that when the R Group was asymmetric the Curtius, Lossen, and Hofmann decompositions did not result in racemization, thus indicating that R migrated as a carbanion. Because of this formal analogy, as noted by Eistert, between these reactions and the Arndt-Eistert rearrangment, Lane, Willenz, Weissberger and Wallis studied the effect on optical activity of the diazoketone rearrangement.

In the two cases studied the results were as follows:

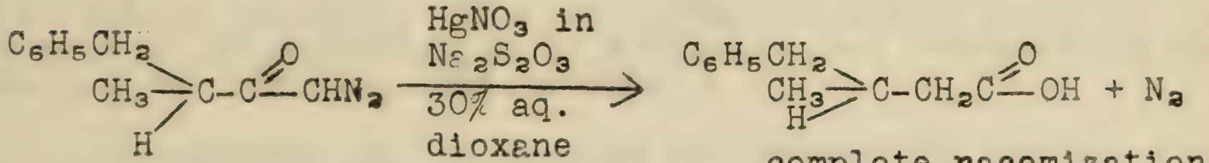
1.



dexter rotatory

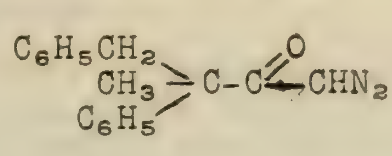
mostly levo rotatory obtained
but some racemization occurred

2.



complete racemization

The diazoketone studied reacted with water in the absence of catalyst to give an active ketoalcohol. The possibility of racemization due to tautomeriaation was ruled out since



which cannot tautomerize, also is racemized during the rearrangement

A possible explanation of this behavior may lie in the migration of the R group wholly or in part as a carbonium ion rather than as the optically more stable carbanion. If the energies required for the two types of ionization were nearly equal, the type of catalyst, and the dielectric constant of the medium would be expected to affect the ionization.

The Arndt-Eistert rearrangement is an excellent means of lengthening the chain of carboxylic acids. It was used by Bachmann in the total synthesis of equilinin. He converted 7-methoxy-2-methyl-2-carbomethoxy-1,2,3,4-tetrahydrophenanthrene-1-acetic acid to the corresponding propionic acid by this method. The methyl ester of this product was cyclyzed and then hydrolyzed to equinilin.

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Reported by Chris Best
November 6, 1940

HIGH-TEMPERATURE CHLORINATION OF PARAFFIN AND OLEFIN HYDROCARBONS

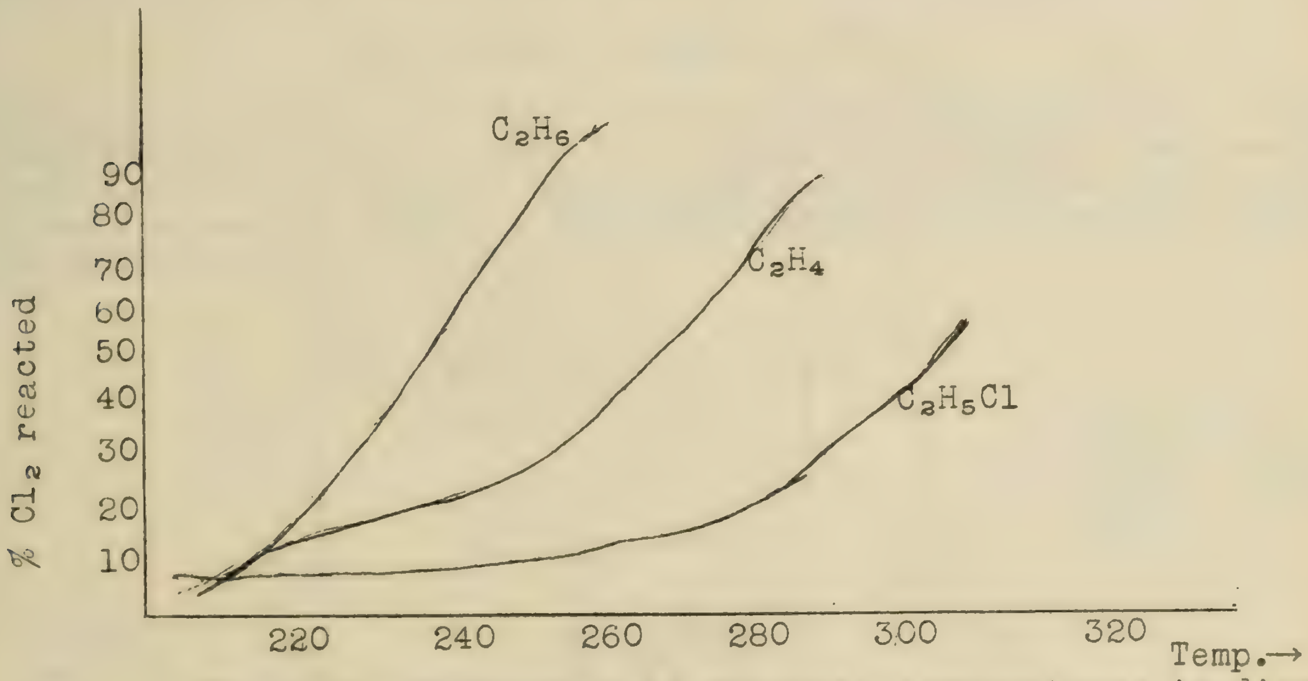
William E. Vaughn and Frederick F. Rust -
Shell Development Company, Emeryville, California

Contrary to classical organic chemistry, Groll and Hearne have found that under certain conditions propylene substitutes rather than adds chlorine. Thus, between temperatures of 400° to 600°C. the halogen in a 1:7 mixture with the olefin is utilized almost entirely by substitution and allyl chloride is the principal product. This can be used as an intermediate in synthesis and consequently the process has far reaching implications.

Development of the process for commercial use has resulted in data from which a mechanism for the reaction may be written. The method has also been applied to paraffin chlorination and the results shall now be discussed.

Chlorination of Paraffins

While the onset of reaction under a given set of conditions for ethane, ethylene and ethyl chloride occurs at approximately the same temperature, the temperature coefficient is much the greatest for ethane and the least for ethyl chloride.



The rate of reaction at moderate temperatures is directly proportional to the concentration of both the paraffin and the halogen.

$$d(HCl)/dt = k\ (Cl_2)(C_2H_6)$$

and a simple mechanism of the following type would apply,

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

$$Cl_2 \rightarrow Cl + Cl$$

$$Cl + C_2H_6 \rightarrow C_2H_5 + HCl$$

$$C_2H_5 + Cl_2 \rightarrow C_2H_5Cl + Cl$$

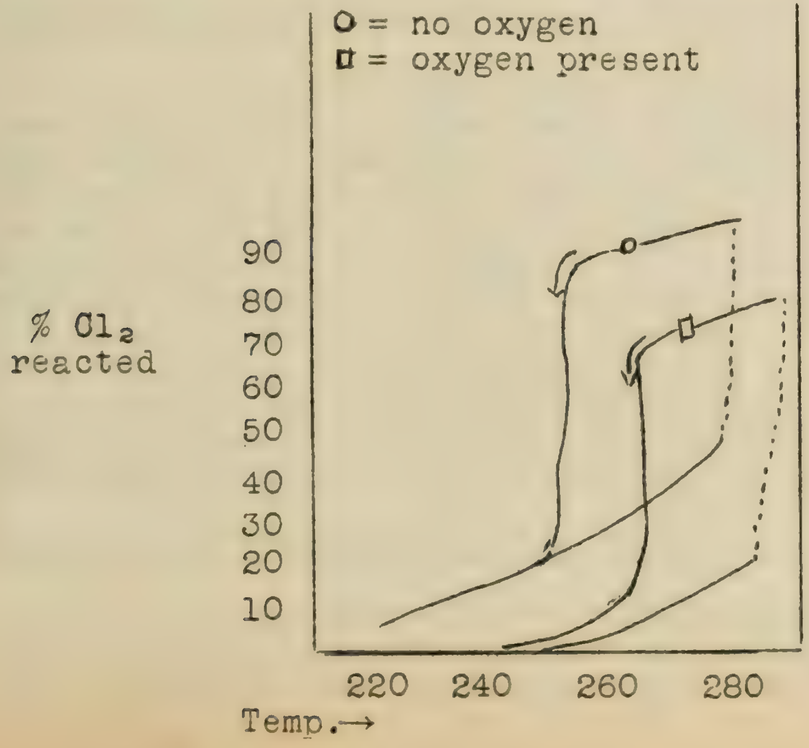
The nature of the inert diluent (N_2, CO_2, or He, mixed with the reacting gases) has little or no effect on the amount of reaction. The chain character of the reaction is demonstrated by the powerful inhibiting effect of oxygen. 20 cc. of oxygen in the flow suppresses all reaction until a temperature of approximately 350°C. is reached. In the absence of oxygen the reaction at this temperature would be uncontrollable.

The chlorination of ethane is highly dependent on the surface which presumably acts to produce chlorine atoms and to terminate chains. Slight increases in surface-volume ratios near the onset temperature result in positive catalysis. However, at higher temperatures some suppression by surface occurs.

Thus far the evidence points to a free radical mechanism, but at high temperatures thermal bimolecular processes are important. In the halogenation of ethane, carried out over glass wool, for example, a very sudden increase in the rate of halogenation occurs at 270 C. The suddenly accelerated reaction may be due to the strong development of thermal chains. Since the reaction,

$$Cl_2 + C_2H_6 \rightarrow C_2H_5Cl + HCl$$

is exothermic (26.8 kilocal.), the uniform dissipation at constant temperature of such an amount of energy constitutes a problem of considerable importance. Under conditions of high reaction newly formed molecules could by collision provide the necessary activation to promote thermal chains.



Chlorination of ethane over glass wool - Effect of oxygen.

In an attempt to clarify the problem of the mechanisms of secondary processes occurring during chlorination of paraffins, the reactivity of ethyl, n-propyl and iso-propyl chlorides has been studied. The reactivities were found to be in the order: n-propyl > iso-propyl > ethyl chloride. Ethyl chloride is much less reactive than ethane. In fact, the amount of chlorine reacting with an ethane-ethyl chloride mixture is approximately that found for pure ethane. Chlorination of ethyl chloride above 280°C. yields large quantities of ethylene and HCl, yet at 415°C. in the absence of halogen there is practically no decomposition. This indicates the splitting off of HCl occurs as an "induced decomposition." The probable reaction is,

$$Cl + EtCl \rightarrow HCl + C_2H_4Cl$$

$$C_2H_4Cl + Cl_2 \rightarrow C_2H_4Cl_2 + Cl$$

At 320°C. the principal products are ethylene, 16.7%; 1,1-dichloroethane, 65.3%; 1,2-dichloroethane, 16.7%.

Hess, McBee and Weber also observed olefin formation during chlorination of paraffins but attribute it to decomposition of alkyl R's yielding H_2 plus the unsaturate.

When ethyl bromide is chlorinated with ethane 0.14 mole of C_2H_4, 0.35 mole of EtCl, 0.95 mole EtBr, and less than 0.04 mole of C_2H_4ClBr resulted. Under the same conditions the amount of C_2H_4 evolved from chlorination of ethane is so very small that it must come about almost entirely from the EtBr. Also the amount of EtCl formed is that expected from the ethane imput and hence the C_2H_4 must come from the EtBr.

In view of these observations, the mechanism of "induced decomposition" seems well established.

Chlorination of Ethane-Ethylene Mixtures

In an ethane-ethylene mixture the ethane is chlorinated almost exclusively. This seems to clarify the mechanism of the high temperature chlorination of propylene. It has been suspected for some time that allyl chloride is formed by direct substitution of the saturated carbon atom of propylene, nevertheless the possibility of the interaction of chlorine with the double bond could not be disregarded, inasmuch as allyl chloride is formed in considerable amounts by pyrolysis of propylene dichloride. The observations with ethane-ethylene eliminate the possibility of a mechanism of addition of one Cl to the one position followed by ejection of an H atom from the three position and shift of the double bond. It now seems certain that direct substitution occurs in the saturated part of the molecule.

Catalysis of Chlorination Reactions

On the basis of the evidence which indicated that high temperature gas phase chlorination of paraffins proceeded by a radical chain mechanism the prediction was made that compounds which decompose

or react readily to give radicals would catalyze certain halogenation processes in the dart, at temperatures below those usually required to initiate reaction. This was found to be true.

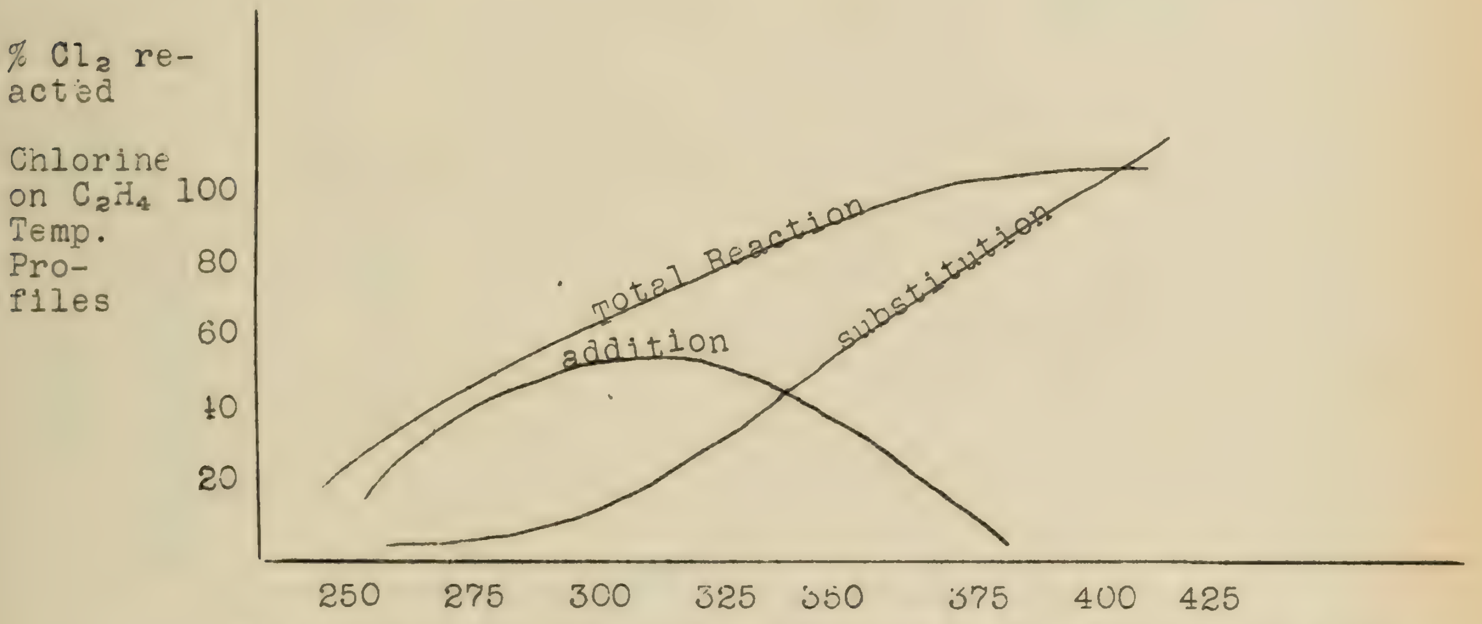
Catalysis by tetraethyl lead

In the presence of lead alkyl more than 95% of the chlorine reacted with ethane at a temperature of 132. Thermal reaction alone requires a temperature of 280-290. Without the lead alkyl no chlorine was consumed. Propane, cyclopentane, and n-pentane all gave the same result. Oxygen suppressed all reaction even in the presence of the catalyst.

Catalysis by Hexaphenylethane and Azomethane

Both show catalytic ability with azomethane the poorer.

Mechanism of Olefin Chlorination Reaction

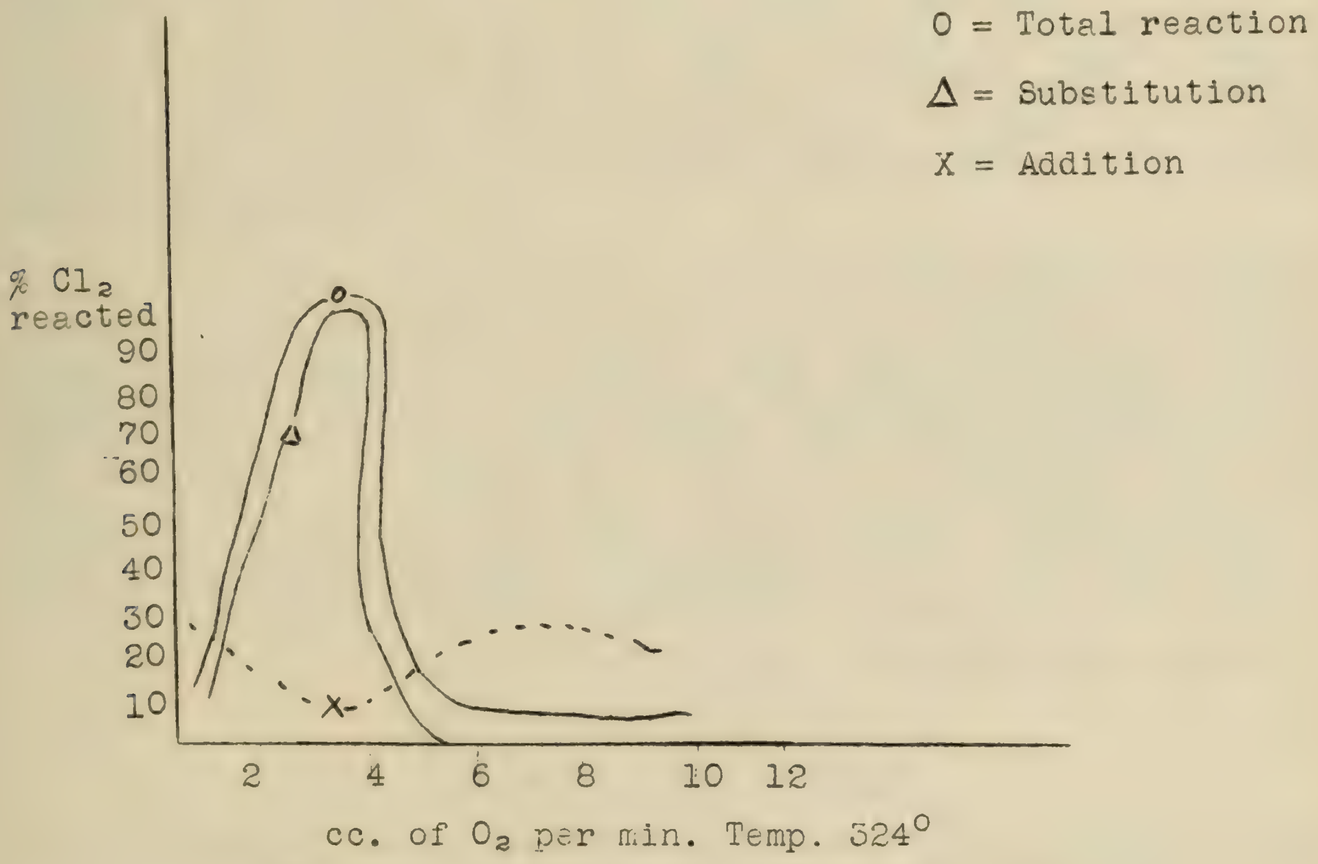


At a given temperature the amount of halogen which goes to addition progressively decreases as the concentration of the reactants increases. This means that while both addition and substitution are highly dependent on the partial pressures of olefin and chlorine, the substitution reaction is of a higher order.

The effect of temperature on substitution is clearly shown by the above curve. 20% of the chlorine is used. The effect of surface on the reaction was the same as observed with paraffins. The chain character of the reaction, under certain conditions, is confirmed by the use of tetraethyl lead as a catalyst. As low as 132°C. in the presence of the catalyst 25% of the total chlorine will substitute. Large amounts of oxygen in the reacting gas suppressed all reaction until a much higher temperature was reached.

Oxygen catalyzed chlorine substitution reactions

The inhibition effect of oxygen on gas phase chlorination reactions has long been known. Consequently, the discovery that, under certain conditions, oxygen strongly catalyzes substitution of chlorine into olefins was quite unexpected. The catalysis for C_2H_4 and C_3H_6 is clearly shown in the following graph. Note that only small amounts of oxygen induce catalysis and large amounts cause the expected inhibition. Two cc. of oxygen per minute cause 87% of the chlorine to substitute while 4 cc. per minute produces a drop to 7%. The effect is less with propane but of the same general character. This catalysis of substitution by oxygen is confined to olefins; no similar effect was found for the paraffins, only inhibition of of chlorination was observed.



Chlorine on ethylene - effect of Oxygen

Chlorination of olefin, oxygen, paraffin mixtures

Ethane is a powerful inhibitor of oxygen catalyzed chlorine substitution into olefins. Ethane in a mole concentration of 15% suppressed substitution in one case from 95% to 13%. The product distribution indicates that ethylene participates only slightly in the reaction: Vinyl chloride 12%, ethyl chloride 60%, 1,1-dichloroethane 16%, 1,1,1-trichloroethane and 1,2-dichloroethane 12%. However, if the olefin is replaced by nitrogen the substitution is reduced below 10%.

An explanation of oxygen catalysis with olefins must take into consideration several facts:

(1) Cl_2 reacts with olefins under conditions formerly considered unfavorable, i.e., in the presence of O_2.
(2) Cl_2 reacts principally by substitution under conditions of temperature which in the absence of oxygen favor additions.
(3) Paraffins (e.g.ethane) inhibit the reaction with the olefin and react with chlorine themselves. Yet no oxygen catalysis of paraffin chlorination is known.
(4) Higher concentration of oxygen strongly inhibit substitution.

These points can be correlated b postulating that the overall rate determining step is the interaction of an oxygen molecule with ethylene (one of two molecules) giving rise to extremely reactive centers which can initiate a chain reaction involving substitution. However, it seems inconceivable that the small amounts of oxygen used could influence the large number of olefin molecules present. Moreover, increasing the oxygen content results in a decrease in reaction though it should produce more of the intermediate complex and, therefore more reaction.

Lenher, in his studies of the oxygen-ethylene reaction, postulated the formation of an association complex which could react with another ethylene molecule to give two molecules of ethylene oxide or with oxygen to give water and carbon monoxide. At higher temperatures he found polymerization products as butenes, propylenes, and amylenes. The formation of the last two suggest that the association complex was capable of dissociation into oxygen and methylene radicals; the latter could react with ethylene or its dimer. In this case a similar production of radicals must be occurring, giving rise to centers which initiate chlorination chains.

$$R + Cl_2 \rightarrow RCl + Cl \quad \text{(R catalytic radical)}$$

$$Cl + C_2H_4 \rightarrow C_2H_3 + HCl$$

$$C_2H_3 + Cl_2 \rightarrow Cl + C_2H_3Cl$$

It is believed, then, that the mechanism is one of chain initiation by radicals produced by interaction of olefin and oxygen rather than reaction of an association complex itself with chlorine.

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Reported by W. J. Gross
November 13, 1940

CONSTITUTION OF ROEMERINE

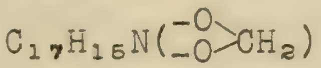
I. Isolation of roemerine.

From the plant Roemera refracta, a member of the papaverine family found in Central Asia, Orekhoff and coworkers (U.S.S.R.) were able to isolate a new alkaloid, presenting itself on initial extraction with ethylene dichloride as a resinous brown mass. The resinous mass gives a slightly soluble crystalline hydrochloride from which the base could be regenerated, m. 102-103°, having the composition $C_{18}H_{17}NO_2$.

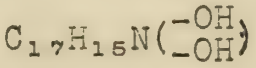
II. Relation to the aporphine series.

The presence of a dioxymethylene group was demonstrated through Gaebel's phloroglucinol and sulfuric acid reaction. In this reaction formaldehyde is split out from the dioxymethylene group by action of concentrated acid. The formaldehyde then reacts with phloroglucinol to give an insoluble red precipitate.

A comparison of the formula of roemerine with that of apomorphine, a member of the aporphine series of alkaloids, shows a striking similarity.



$C_{17}H_{15}N(\genfrac{}{}{0pt}{}{-O}{-O}{>}CH_2)$



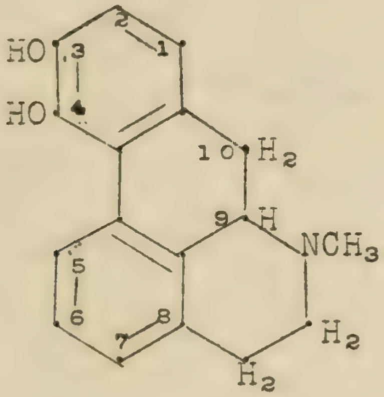
$C_{17}H_{15}N(\genfrac{}{}{0pt}{}{-OH}{-OH})$

roemerine

apomorphine

It has been demonstrated that apomorphine and all other members of the aporphine series have a phenanthrene-isoquinoline nucleus. Thus the structural formula for apomorphine is-

I

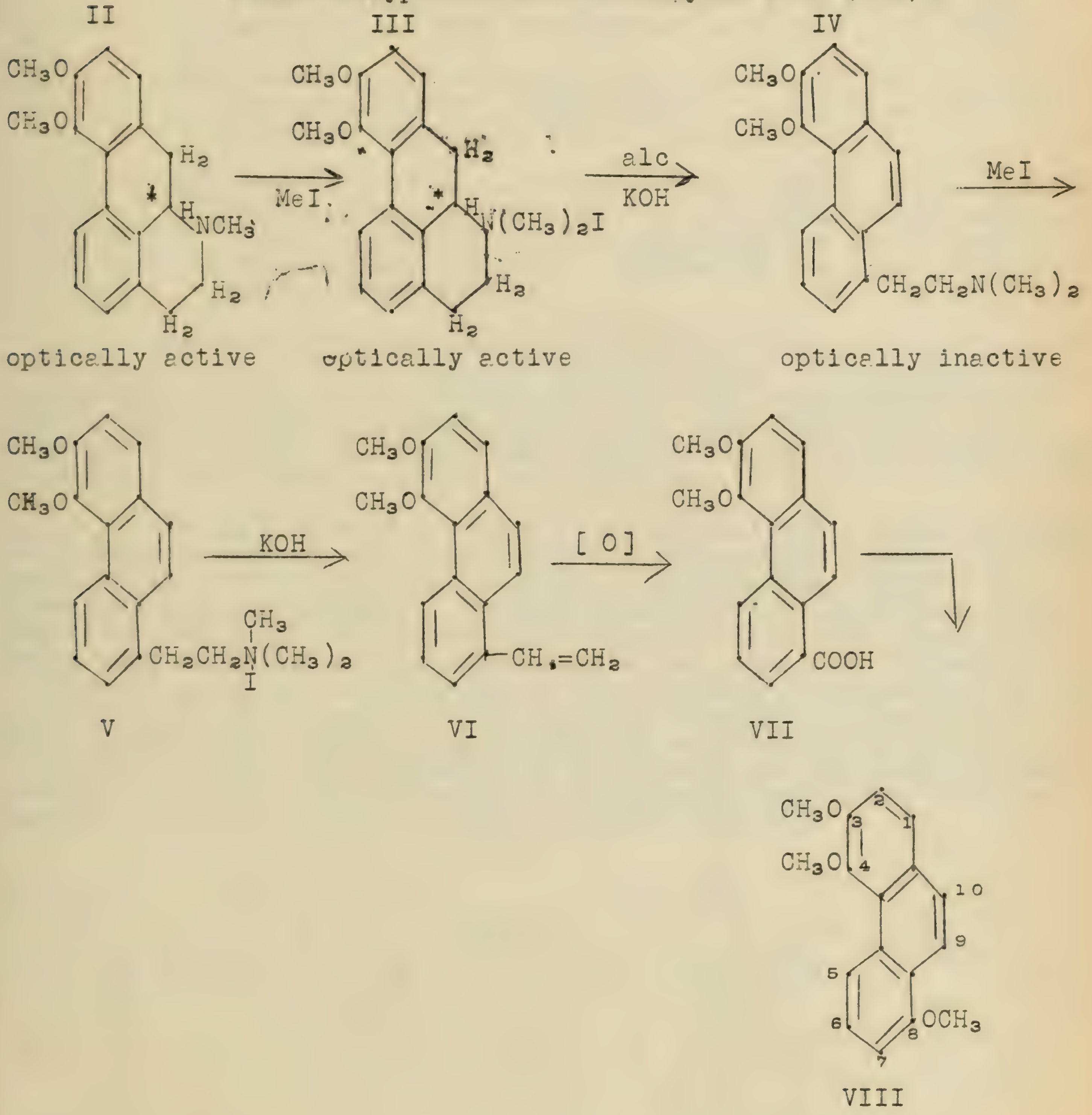


The phenanthrene-isoquinoline nucleus of apomorphine has been demonstrated by Pschorr both by degradation (1907) and by synthesis (1929). A brief outline of his evidence follows.

(1) Distillation of apomorphine with zinc dust gave phenanthrene.

(2) Apomorphine (I) was transformed into the dimethyl ether by treatment of its hydrochloride with diazomethane in amyl alcohol solution. This ether (II) was subjected to the Hofmann degradation. Thus with methyl iodide

the methiodide (III) was formed which on warming with alcoholic sodium hydroxide gave an optically inactive base (IV). Alcoholic potassium hydroxide caused a splitting of the methiodide (V) of the base (IV) into trimethyl amine and a nitrogen free unsaturated phenanthrene derivative (VI). Oxidation of the latter phenanthrene derivative with calcium permanganate gave a dimethoxyphenanthrenecarboxylic acid (VII).



[illegible]

These results are interpreted as follows:

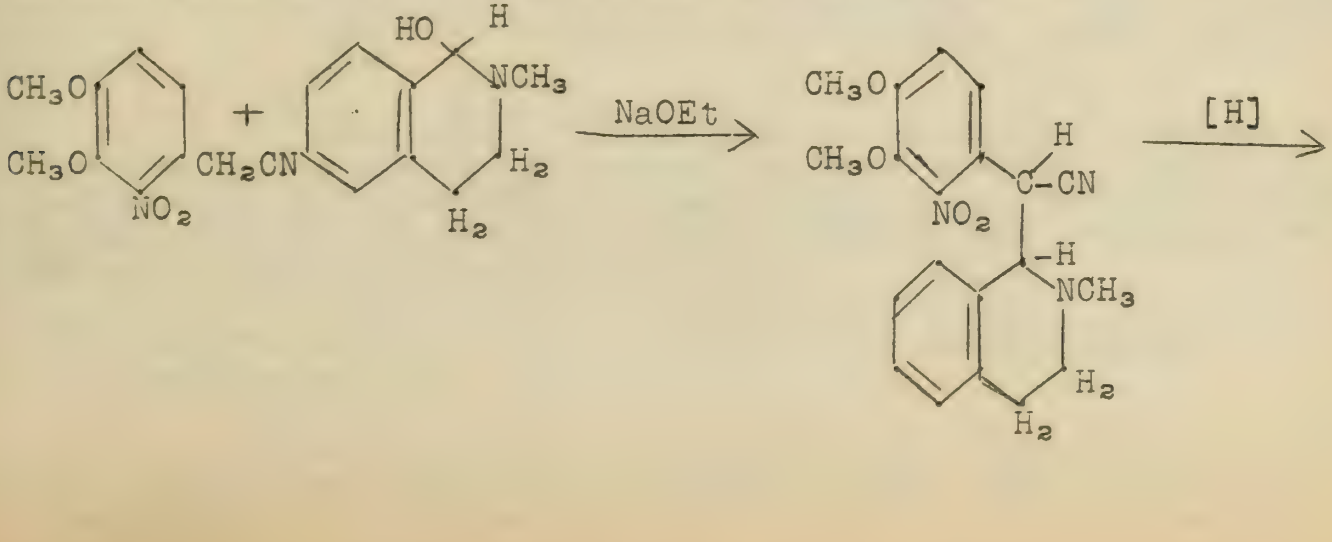
(1) Loss of optical activity on treatment of the methiodide (III) with alcoholic KOH indicates that the nitrogen atom was tertiary and that a splitting had occurred between the nitrogen atom and an asymmetric carbon atom. Since the nitrogen remains as a part of the molecule, it must have formed part of a ring system.

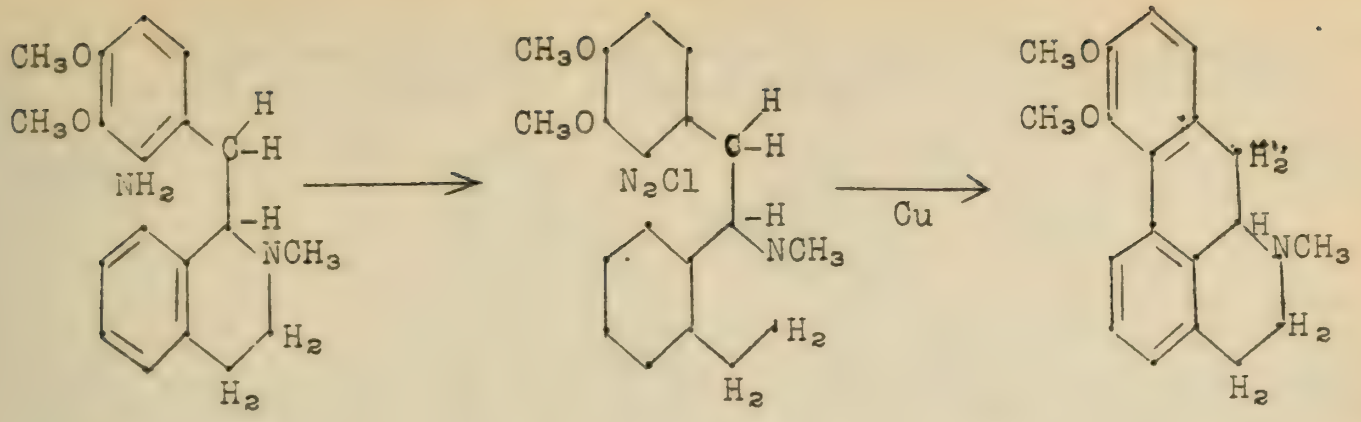
(2) Production of trimethylamine as a result of the fourth degradation step (from V to VI) is evidence that the nitrogen originally held a $-CH_3$ group.

(3) Formation of an unsaturated phenanthrene compound (VI), followed by its oxidation to a phenanthrenecarboxylic acid, together with the evidence given above, demonstrates that the group $-CH_2CH_2NCH_3-$ is attached to the phenanthrene nucleus.

Pschorr converted the dimethoxyphenanthrenecarboxylic acid (VII) to the amine by the Curtius rearrangement. The amine was converted into the diazonium chloride and the latter decomposed to the phenol which in turn was methylated to give the ether. The trimethoxyphenanthrene thus formed was found to be identical with 3,4,8-trimethoxyphenanthrene synthesized by Pschorr(VIII).

In 1929 Pschorr and Avenarius synthesized a compound having the structure Pschorr had postulated for apomorphine in 1910 on the basis of the above work. The synthetic compound was found to be identical with apomorphine. In this synthesis they proceeded from 2-nitrobenzoyl cyanide and α-hydroxy-N-methyl tetrahydroisoquinoline. These were condensed by the action of sodium ethylate. Hydrolysis of the -CN group and elimination of CO_2, followed by reduction of the nitro group, gave an amine which could be converted by the Pschorr phenanthrene ring closure to the apomorphine dimethyl ether (IX). Identification was made through the methiodide and the methine base derived therefrom. All attempts to racemize l-apomorphine for comparison with the synthetic racemic compound failed.





IX

We have seen that there is a resemblance between the empirical formulas of roemerine and apomorphine. Evidence that both actually do have the same nucleus is:

(1) Distillation of roemerine with zinc dust gives phenanthrene.

(2) Degradation of roemerine presents a series of steps absolutely analagous to the degradation steps of apomorphine, bulbocapnine, and other alkaloids of the aporphine series. At each step the nature and composition of the compound isolated is exactly that which would be expected were an aporphine nucleus undergoing degradation.

Thus, the methiodide of roemerine gives on warming with alcoholic KOH a new base, $C_{19}H_{19}NO_2$, crystals, m. 73-74°, optically inactive.

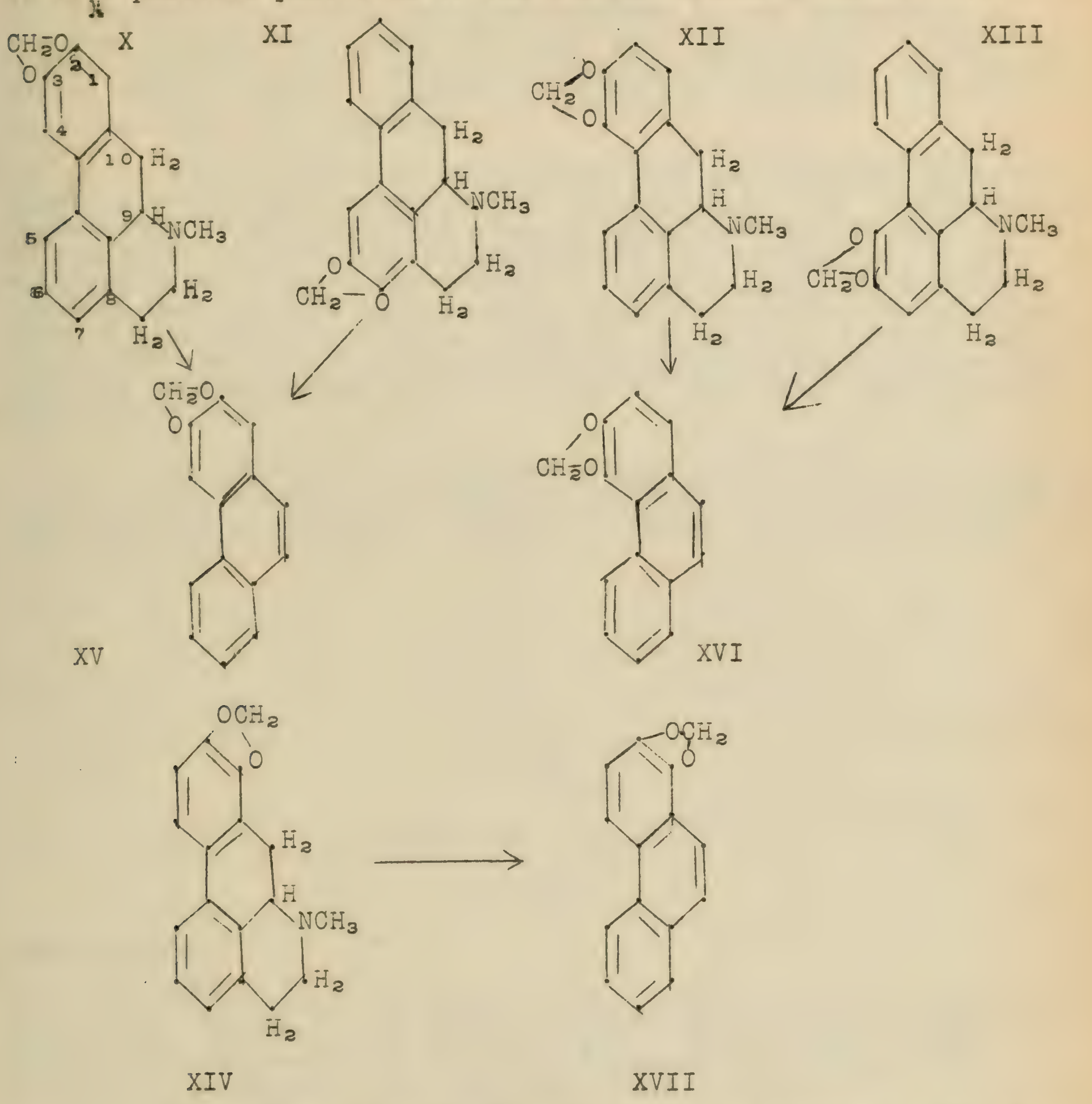
Treatment of the methiodide of this last base with alcoholic KOH causes a splitting into trimethylamine and a crystalline compound no longer containing nitrogen, m. 86-87°. The latter compound was distinctly unsaturated and could be oxidized by permanganate to a crystalline acid, $C_{16}H_{10}O_4$, m.263-4°. Elimination of CO_2 from the latter acid could be effected by heating the acid in quinoline with Adkins copper chromite catalyst.

The conversion of roemerine to phenanthrene on heating with zinc dust and a course of degradation corresponding exactly to the degradation of the aporphine alkaloids was considered sufficient evidence by the investigators for concluding that roemerine was a member of the aporphine series.

III. Determination of the position of the dioxymethylene group in roemerine.

Assuming that roemerine does have an aporphine nucleus, all that is left for complete elucidation of the constitution of roemerine is establishment of the position of the dioxymethylen

group. There are five possible formulas for roemerine corresponding to five possible positions of the dioxymethylene group (X-XIV).



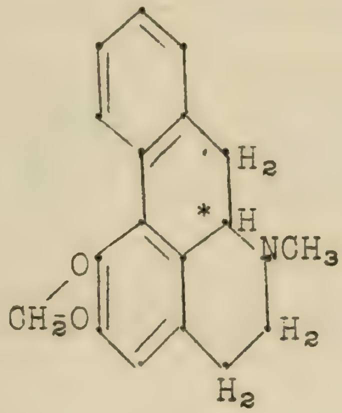
2,3 and 6,7-dioxymethyleneaporphine (X and XI) give by degradation the same product, namely 2,3-dioxymethylenephenanthrene (XV). For comparison with the actual degradation product of roemerine, m. 86-87°, 2,3-dioxymethylenephenanthrene was prepared for the first time. It melted at 99-100°, and its non-identity with degradation product of roemerine was definitely demonstrated. Thus formulas X and XI are excluded as possible formulas for roemerine.

Hydrolysis of the dioxymethylene group by phloroglucinol and sulfuric acid gave a diphenolic base, $C_{17}H_{17}NO_2$, having one of three possible formulas corresponding to XII, XIII, and XIV in which the dioxymethylene group has been replaced by two hydroxyls. A compound having the formula XII would give apomorphine on hydrolysis, but the diphenolic base actually obtained differs from apomorphine. Hence, formula XII is excluded as a possible structure. The new base was named nor-roemerine.

Nor-roemerine by methylation with diazomethane gives the dimethyl ether, non-identical with the dimethyl ether of apomorphine. Degradation of this dimethyl ether of nor-roemerine by the Hofmann method leads to a dimethoxyvinylphenanthrene. Oxidation of this compound gives a dimethoxycarboxylic acid, $C_{17}H_{14}O_4$, m. 212-213°, which on heating with Adkins copper chromite catalyst in quinoline gives a dimethoxyphenanthrene, $C_{16}H_{14}O_2$, m.43-44°. A direct comparison of the latter compound with 3,4-dimethoxyphenanthrene (XVI with the dioxymethylene group replaced by methoxyls) demonstrated their identity.

3,4-Dimethoxyphenanthrene could be obtained from XII as well as XIII, but XII has already been ruled out (non-identity of nor-roemerine and apomorphine). Hence it follows that roemerine must be 5,6-dioxymethyleneaporphine (XIII).

XIII



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Reported by T. E. Calmes
November 13, 1940

KETENE ACETALS

McElvain et al. - University of Wisconsin

The first method used for making ketene acetals consisted in heating ortho esters.

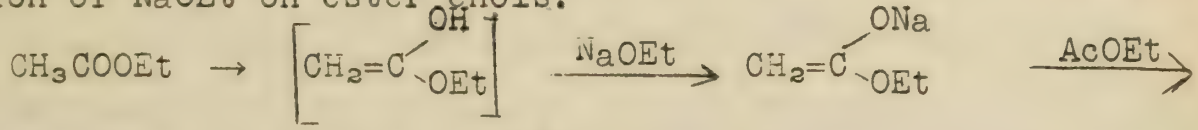
$$CH_3C(OR)_3 \rightarrow CH_2{=}C(OR)_2 + ROH$$

In this way, Biginelli prepared ketene diphenyl acetal, $CH_2{=}C(OC_6H_5)_2$, and Reitter and Weindel prepared carbethoxy ketene diethyl acetal, $C_2H_5O_2CCH{=}C(OEt)_2$.

Standinger found that not all ortho esters were easily converted to ketene acetals. However, triethyl ortho phenyl acetate readily produced the ketene acetal -

$$C_6H_5CH_2C(OEt)_3 \xrightarrow[12\ mm.]{\Delta} C_6H_5CH{=}C(OEt)_2 + EtOH$$

Scheibler claimed that ketene acetals often resulted from the action of NaOEt on ester enols.



$$CH_3COOEt \rightarrow \left[CH_2{=}C\begin{matrix}OH\\OEt\end{matrix}\right] \xrightarrow{NaOEt} CH_2{=}C\begin{matrix}ONa\\OEt\end{matrix} \xrightarrow{AcOEt}$$

$$CH_3COCH_2C(OEt)_2(ONa) \xrightarrow{H^+} CH_2{=}C(OEt)_2 + CH_3COOH$$

Scheibler found that his product had a boiling point of 77.5-78.0°. McElvain pointed out that the boiling point should be much higher. Moreover, careful examination of the product boiling from 77-78° showed that it was a mixture of ethyl alcohol and ethyl acetate.

One of the obvious routes to the synthesis of ketene acetals involves the elimination of HX from a halogenated acetal (I) by means of alcoholic alkali.

I $XCH_2CH(OEt)_2$
II $CH_2{=}C(OEt)_2$
III $HOCH_2CH(OEt)_2$
IV $CH_3C(OEt)_3$

McElvain found that alcoholic KOH and the chloroacetal, I, gave the acetal of glycolic aldehyde III in 95% yield. With the bromo- and iodo- acetals, III was also formed in 70% and 30% yields. The remainder of the product consisted of a mixture of ethyl acetate and ethyl ortho acetate, IV. These esters of acetic acid show that some elimination took place from the bromo compound and that it was the major reaction in the case of the iodoacetal. The ketene acetal, II, must have been an intermediate, adding H_2O or EtOH to give ethyl acetate and ethyl ortho acetate.

The solvent evidently was too active to permit isolation of the ketene acetal. Therefore, a less reactive medium was sought. Potassium tert.-butoxide in tert.-butyl alcohol proved to be the

most satisfactory since the reaction took place at the boiling point. The ketene diethyl acetal was separated by fractionation and had a boiling point of 124-126°; higher than acetal as McElvain had predicted.

The halogenated ketene acetals were prepared in the same way as the unsubstituted acetal. The first one resulted from an attempt to prepare tetraethoxy ethylene:

$$\begin{array}{l} Br_2CHCH(OEt)_2 \xrightarrow{KOEt} Br(OEt)CHCH(OEt)_2 \\ \qquad \qquad \qquad \longrightarrow BrCH{=}C(OEt)_2 \xrightarrow{EtOH} BrCH_2C(OEt)_3 \end{array}$$

Using potassium tert.-butoxide as solvent, $BrCH{=}C(OEt)_2$ was prepared in 82% yield.

The monochloro-, dichloro- and dibromo-ketene acetals were also prepared by elimination of HX. The tribromoacetal was prepared by bromination of the dibromo compound and the trichloroacetal from chloral alcoholate:

$$CCl_3CH(OH)(OEt) \xrightarrow{PCl_5} CCl_3CHCl(OEt) \xrightarrow{HOEt} CCl_3CH(OEt)_2$$

Another route to the ketene acetal structure is the elimination of the elements of ethyl hypohalite, EtOX from an α-halogeno ortho acetic ester in a manner similar to that used by Boord and coworkers to prepare olefins. Sodium was substituted for Zn or Mg and a general method for substituted ketene acetals in yields as high as 80% was the result.

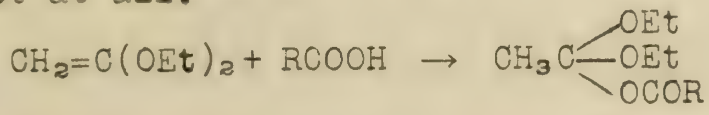
$$RCHBrC(OEt)_3 + 2Na \longrightarrow RCH{=}C(OEt)_2 + NaBr + NaOEt$$

The outstanding reactions of ketene diethylacetal are those of addition. The most important are:

1. $CH_2{=}C(OEt)_2 + H_2O \rightarrow CH_3COOEt + HOEt$

2. $CH_2{=}C(OEt)_2 + HOEt \rightarrow CH_3C(OEt)_3$

Secondary alcohols behave similarly, but tertiary alcohols do not react at all.

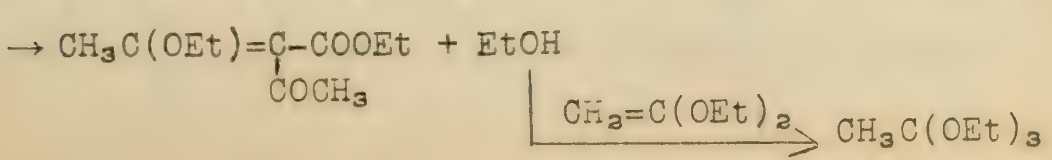
3. 

$$CH_2{=}C(OEt)_2 + RCOOH \rightarrow CH_3C\begin{cases} OEt \\ OEt \\ OCOR \end{cases}$$

4. $CH_2{=}C(OEt)_2 + HX \rightarrow CH_3C(OEt)_2X$

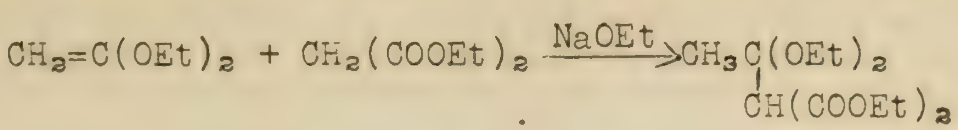
5. $CH_2{=}C(OEt)_2 + C_6H_5OH \rightarrow CH_3C(OEt)_2(OC_6H_5)$

6. $CH_2{=}C(OEt)_2 + CH_3COCH_2COOEt \rightarrow CH_3C(OEt)_2CH(COCH_3)COOEt$

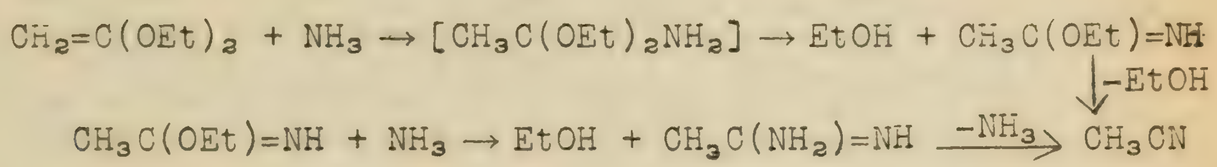


$$\rightarrow CH_3C(OEt){=}\underset{\displaystyle COCH_3}{C}{-}COOEt + EtOH \xrightarrow{CH_2=C(OEt)_2} CH_3C(OEt)_3$$

The use of NaOEt greatly increased the yield of the product in the above reaction and was absolutely necessary for malonic ester.

7. 

$$CH_2{=}C(OEt)_2 + CH_2(COOEt)_2 \xrightarrow{NaOEt} \underset{CH(COOEt)_2}{CH_3C(OEt)_2}$$

8. 

$$\begin{tikzcd}[column sep=small] CH_2{=}C(OEt)_2 + NH_3 \arrow[r] & {[CH_3C(OEt)_2NH_2]} \arrow[r] & EtOH + CH_3C(OEt){=}NH \arrow[d, "-EtOH"] \\ CH_3C(OEt){=}NH + NH_3 \arrow[r] & EtOH + CH_3C(NH_2){=}NH \arrow[r, "-NH_3"] & CH_3CN \end{tikzcd}$$

Aniline gives the corresponding phenyl substituted products but it reacts more vigorously.

9. $2CH_2{=}C(OEt)_2 + EtNHC_6H_5 \rightarrow CH_2{=}C(OEt)N(Et)C_6H_5 + CH_3C(OEt)_3$

10. $2CH_2{=}C(OEt)_2 + 3HNC_5H_{10} \rightarrow CH_3C(NC_5H_{10})_3 + CH_3C(OEt)_3 + EtOH$

11. $CH_2{=}C(OEt)_2 \xrightarrow[Ni]{[H]} CH_3CH_2(OEt)_2$ 35%

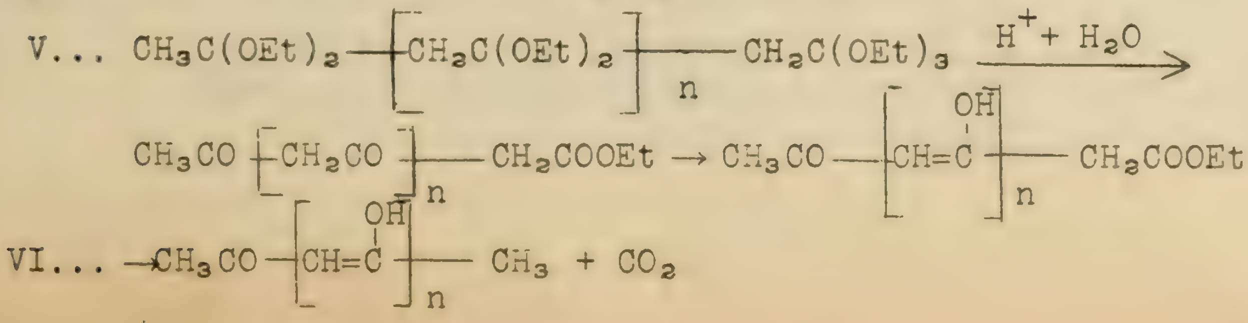
12. Ketene diethylacetal even adds to itself in the presence of cadmium chloride, forming the dimer, $CH_3C(OEt)_2CH{=}C(OEt)_2$, which was converted to ethyl acetoacetate by 95% alcohol and a trace of acid. Two trimers were formed, one of which the authors proved to be $CH_3C(OEt)_2CH_2C(OEt)_2CH{=}C(OEt)_2$.

13. Polymerization. By using a small amount of a catalyst, such as an acid or various metal chlorides, the addition of ketene acetal to itself is promoted so that polymers result. Cadmium chloride as a catalyst gave a stable white polymer.

The carbon and hydrogen content of this polymer is practically the same as that of the monomer but the ethoxyl value is low. The polymer is stable to heat and alkali but very sensitive to acids. Dilute acids change it to a red oil and refluxing with acid yields a reddish-black oil cooling to a brittle glass.

Previous work on unsymmetrically substituted ethylenes would seem to predict a polymerization in a "head to tail" manner. This was supported by properties of the red polymer. The color and alkali solubility indicate a poly-1,3-diketone in an enolic and highly conjugated state.

The white and red polymers may be represented by V and VI on basis of "head to tail" polymerization.



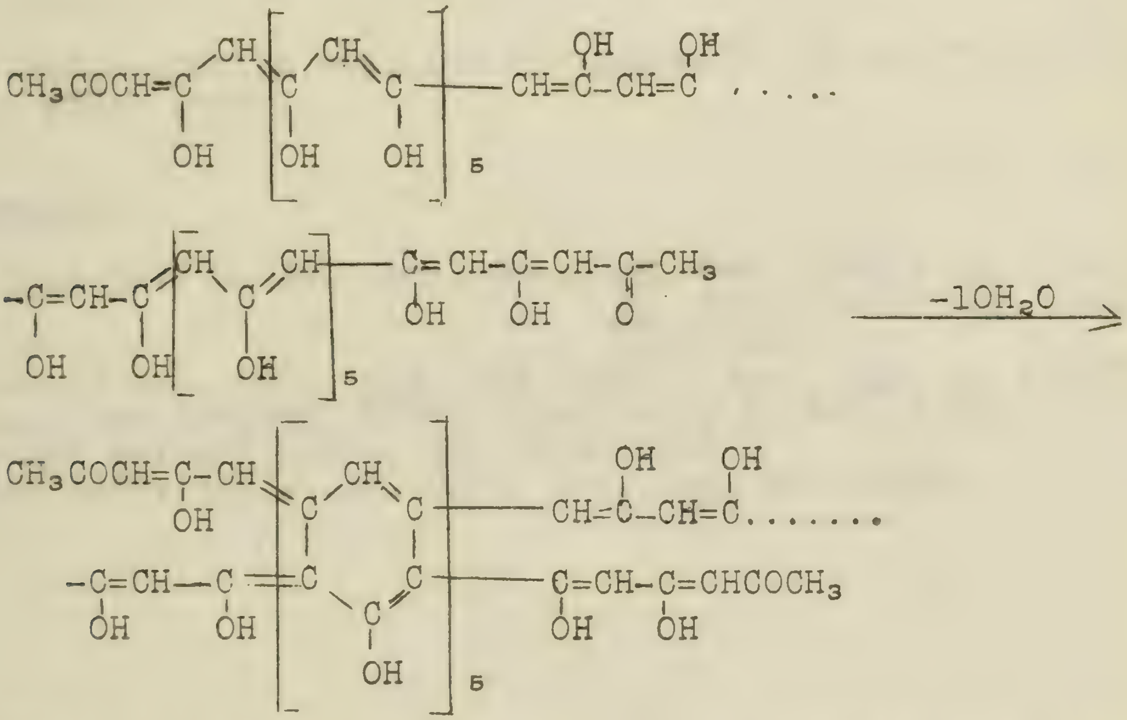
$$V\ldots\ CH_3C(OEt)_2 \left[CH_2C(OEt)_2 \right]_n CH_2C(OEt)_3 \xrightarrow{H^+ + H_2O}$$

$$CH_3CO \left[CH_2CO \right]_n CH_2COOEt \rightarrow CH_3CO \left[CH{=}\overset{OH}{C} \right]_n CH_2COOEt$$

$$VI\ldots \rightarrow CH_3CO \left[CH{=}\overset{OH}{C} \right]_n CH_3 + CO_2$$

The value of n obtained from CO_2 evolved as shown in the above reaction to produce VI indicated a molecular weight of 2600-2700 with n=20-21. Lack of solubility in any organic solvent gives evidence for some cross linking but the extent is small.

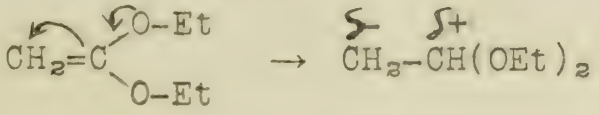
The analyses of the red polymer suggest an empirical formula of $C_{45}H_{38}O_{17}$ instead of $C_{45}H_{48}O_{22}$ which VI would have if n = 21. Here it seems that cross linking must have occurred resulting in the loss of an average of 5 molecules of H_2O per unit of VI. The end methyl groups are probably not involved and the molecule should be:



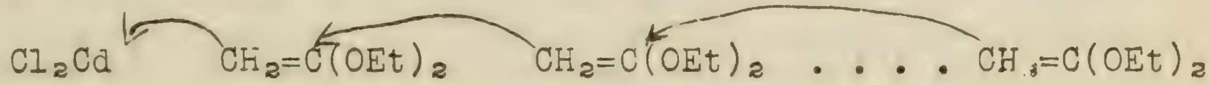
The color of the red polymer is due to its high conjugation since hydrogenation carried out in alkaline solution of the polymer with Raney nickel at 225° and 200 Atm. removes the red color.

Oxidation of the polymer with nitric acid gave no succinic acid. Permanganate oxidation gave the amount of acetic acid expected from the above formula.

The mechanism of polymerization is suggested by the structure of the acetal. It is an unusual hetero-enoid system in that two very effective hetero atoms, oxygen, are attached to the same carbon atoms carrying a double bond. An anionoid center is built upon the methylene carbon.



It will therefore tend to add protons. The negative portion will add to the other carbon atom. The coordination of the highly polar methylene group with the cadmium chloride initiates a chain reaction which may be propogated in the following manner:



$Cl_2Cd \quad CH_2{=}C(OEt)_2 \quad CH_2{=}C(OEt)_2 \; . \; . \; . \; . \; CH_2{=}C(OEt)_2$

Addition of a proton and the ethoxyl group from EtOH to the ends of the polymer would release the catalyst and saturate the ends of the chain.

This mechanism explains the formation of the "head to tail" polymers given above.

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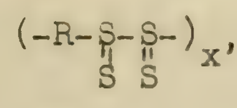
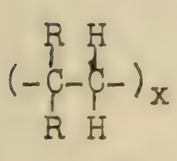
Reported by John Lawler
November 20, 1940

ARTIFICIAL RUBBER

M. L. Denivelle; Ecole Superieure de Chimie de Mulhouse

"Artificial rubber" designates any synthetic material possessing rubber-like elasticity and usable to partly replace natural rubber. Included are compounds with molecular weights of the order of 100,000 and the following structural units:

$(-CH_2-CR-CH-CH_2-)_x$	Butadiene type, R=H, Cl
 $(-\mathrm{R}-\underset{\substack{\| \\ \mathrm{S}}}{\mathrm{S}}-\underset{\substack{\| \\ \mathrm{S}}}{\mathrm{S}}-)_x$, $(-R-S_3-)_x$, $(-R-S_2-)_x$	Organic polyhalogen type. R = almost any organic dihalide.
 $(-\underset{\mathrm{R}}{\overset{\mathrm{R}}{\mathrm{C}}}-\underset{\mathrm{H}}{\overset{\mathrm{H}}{\mathrm{C}}}-)_x$	Butyl rubber type. R = CH_3, perhaps hydrogen and other groups as well.

Only these structures have given important synthetic rubbers.

Relation of elasticity and structure

According to Meyer elastic compounds contain long, pliable molecules which are twisted and intertwined in a complicated manner. At rest the arrangement is haphazard, but on stretching material containing these molecules, they are straightened in the direction of the stretching. Retraction on decrease of the stretching force is considered as due to the tendency of these molecules to return to their most probable length. Returning force is proportional to the absolute temperature. Slight cross-linking, as in the case of vulcanized rubber, would not interfere with this process.

Mack has developed another theory in which the retracting force is treated as due to the Van der Waal's forces between hydrogen atoms in the rubber molecule. When at rest, the molecules are folded so that these forces are at a maximum; on stretching the rubber the folded molecules also stretch, or unfold, so that the forces decrease.

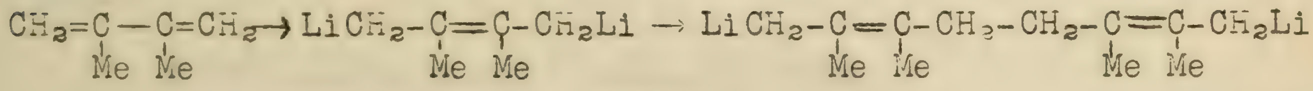
The similarity of X-ray diffraction patterns given by various stretched elastic compounds indicates a similar fine structure. Such a similarity is generally accepted although neither of the above theories is widely held. Many other explanations have proved untenable, most of them because of assumptions that elasticity was related to the presence of unsaturated linkages. Recent work by Sparks et al. indicates that high chemical reactivity is the only property of rubber related to its double bonds. For example, butyl rubber exhibits most of the properties of natural rubber but is saturated.

Methods of polymerization

The organic polysulfides are synthesized directly as compounds of high molecular weight. Butadiene and butyl rubbers are made by polymerization of low molecular weight hydrocarbons. Below are the important methods.

1. Polymerization by use of metallic sodium.

The Buna 85 and 115 rubbers are formed from butadiene by this method. The properties of the polymer may be changed by varying the temperature or adding an inert diluent such as benzene. Using lithium as catalyst Zeigler isolated intermediates which showed polymerization of dimethylbutadiene to proceed by formation of active organometallic compounds:



$$CH_2{=}\underset{Me}{C}-\underset{Me}{C}{=}CH_2 \rightarrow LiCH_2-\underset{Me}{C}{=}\underset{Me}{C}-CH_2Li \rightarrow LiCH_2-\underset{Me}{C}{=}\underset{Me}{C}-CH_2-CH_2-\underset{Me}{C}{=}\underset{Me}{C}-CH_2Li$$

Use of a catalyst such as diazoaminobenzene may greatly decrease the time and temperature required for polymerization.

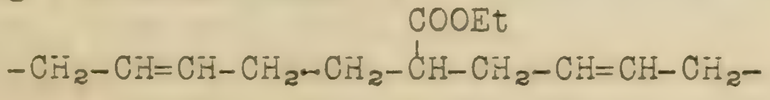
2. Polymerization in emulsion.

Examples of rubbers formed by polymerization of dienes in aqueous suspension are Perbunan and some kinds of Neoprene. The emulsions are formed with the aid of common emulsifying agents such as alkali salts of oleic or stearic acids, alkylnaphthalene sulfonates, etc., and may be stabilized by the use of protective colloids like gum arabic, albumin, or dextrin. Such emulsions polymerize at slightly increased temperature in the presence of catalysts. Oxidizing agents are most effective. An artificial latex is formed, which may be coagulated.

3. Autopolymerization, by simple standing or heating is now used only in the polymerization of chloroprene. This compound polymerizes some 700 times as fast as butadiene. Usually the polymerization of chloroprene is carried out in the presence of a diluent such as benzene or carbon tetrachloride to form a plastic rather than an elastic product.

Copolymerization

Almost any of the materials which ordinarily form plastics on polymerization may be incorporated in large proportions in diene rubbers. By adding ethyl acrylate to butadiene, chains of the following structure result:



$$-CH_2-CH{=}CH-CH_2-CH_2-\overset{COOEt}{CH}-CH_2-CH{=}CH-CH_2-$$

The foreign component may amount to 40 per cent or more by weight of the finished product and may change entirely the properties of the rubber. Solubility, resistance to swelling, and chemical properties are especially altered. Perbunan, containing acrylonitrile, is very resistant to swelling by oils.

Transformation of plastic polymers into elastic polymers

Like natural rubber, the products of polymerization in the manufacture of artificial rubber are only slightly elastic. In this state they may be mixed, molded, and handled easily. Natural rubber is made elastic by vulcanization with sulfur added. The unsaturation is diminished by this treatment and cross-linking seems to take place. Butadiene rubbers are vulcanized exactly as natural rubber. Butyl rubber contains a sufficient quantity of dienes so that on vulcanization a saturated product is obtained. Neoprene is vulcanized by simple heating, at 100°-160°, in the presence of zinc salts, ferric chloride, or primary aromatic amines. The organic polysulfides also undergo a kind of vulcanization by simple heating at a temperature of 130°-150° C.

Preparation of artificial rubbers

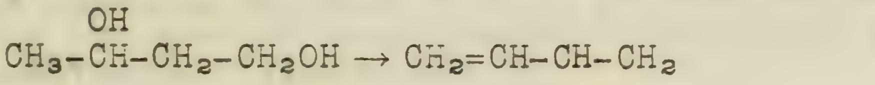
As sources of the many marketed artificial rubbers only a few compounds are used. The preparation of the most important of these follows:

1. Butadiene.

As base for the Buna rubbers this compound is prepared in Germany using acetylene as starting material.

$$HC{\equiv}CH \rightarrow CH_3CHO \rightarrow CH_3CHCHCH_2CHO \rightarrow CH_3CHOHCH_2CH_2OH$$

The 1,3-butylene glycol is catalytically dehydrated, to give a very pure product:



$$CH_3\text{-}\underset{}{\overset{OH}{CH}}\text{-}CH_2\text{-}CH_2OH \rightarrow CH_2{=}CH\text{-}CH\text{-}CH_2$$

In Russia, SKA rubber is prepared by polymerization of butadiene from the cracking of hydrocarbons. The diene is purified through formation of its addition compounds with sulfur trioxide or with certain metal salts.

SKB rubber is produced from butadiene prepared by the Lebedew method, beginning with alcohol produced by fermentation. This is much more important than the cracking process. When the ethyl alcohol is passed over a mixed catalyst at a temperature of 400°-500°C. both dehydration and dehydrogenation take place in a very complex reaction. The yield contains 75 to 80 per cent butadiene plus about 15 per cent pseudobutylene, and by-products including hydrogen, carbon monoxide, and many hydrocarbons, alcohols, aldehydes, ketones, and esters are produced. Traces of aldehydes or ketones in the butadiene hinder or stop polymerization, making the purification of the diene a difficult matter. To improve the yield the pseudobutylene is often reworked to give butadiene by one of the two processes:

The foreign component may amount to 40 per cent or more by weight of the finished product and may change entirely the properties of the rubber. Solubility, resistance to swelling, and mechanical properties are especially altered. [illegible], containing [illegible], is very resistant to swelling by oils.

Depolymerization of plastic polymers into elastic polymers

Like natural rubber, the products of polymerization in the manufacture of artificial rubber are only slightly elastic. In this state they may be mixed, molded, and worked easily. Natural rubber is made elastic by vulcanization with sulfur. The [illegible] is diminished by this treatment and cross-linking seems to take place. Synthetic rubbers are vulcanized exactly as natural rubber. Butyl rubber contains a sufficient quantity of [illegible] that vulcanization [illegible] product is [illegible]. Neoprene is vulcanized by simple heating, or [illegible] the [illegible] of zinc oxide, ferric chloride, or primary aromatic amines. The organic [illegible] undergo a kind of vulcanization by simple heating at a temperature of 130-150° C.

Preparation of [illegible]

At present [illegible] of the most important artificial rubbers only a few compounds are used. The preparation of [illegible] are described [illegible].

1. Butadiene.

[illegible]

[illegible]

The 1,3-butylene [illegible] to give a very good product:

[illegible]

In Russia, the butadiene is prepared by [illegible] from the [illegible] of [illegible]. [illegible]

The butadiene is [illegible] method, beginning with alcohol obtained by fermentation. [illegible] at a temperature of 400-450° C. [illegible] place is a very [illegible]. The yield [illegible] per cent [illegible] and by-products [illegible] butylene, [illegible] are produced. [illegible] separation [illegible] is [illegible]. [illegible]

(a) Passing over difficultly reducible oxides at 700-800°C.

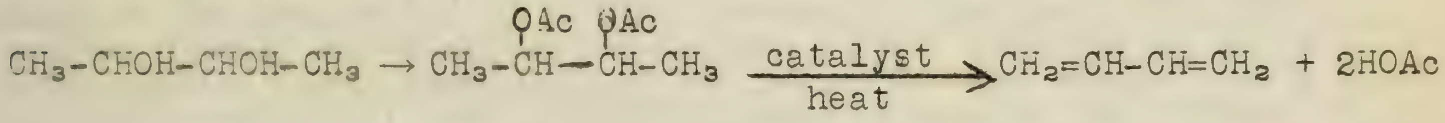
$$CH_3-CH=CH-CH_3 \rightarrow CH_2=CH-CH=CH_2$$

(b) Chlorination with subsequent removal of HCl.

$$CH_3-CH=CH-CH_3 \rightarrow CH_3-CHCl-CHCl-CH_3 \rightarrow CH_2=CH-CH=CH_2$$

About 750 pounds of SKB rubber are produced per ton of alcohol used.

In France and England the production of butadiene from pseudobutylene glycol, obtained by fermentation, has been worked out experimentally. Simple dehydration of this compound leads to methylethylketone, but when the acetate is used as intermediate the reaction proceeds very smoothly:



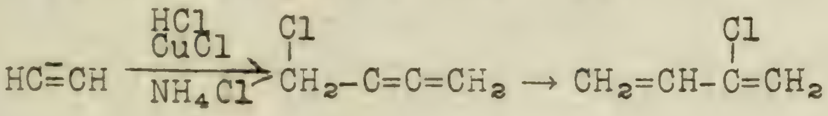
$$CH_3-CHOH-CHOH-CH_3 \rightarrow CH_3-\overset{OAc}{\overset{|}{C}}H-\overset{OAc}{\overset{|}{C}}H-CH_3 \xrightarrow[heat]{catalyst} CH_2=CH-CH=CH_2 + 2HOAc$$

The production of butadiene in America will probably involve dehydrogenation cracking. This may be carried out under reduced pressure at temperatures around 600° with the use of chromium, vanadium, or molybdenum oxides as catalysts. The formation of butadiene from pseudobutylene is an example.

2. Chloroprene

Chloroprene was first produced commercially in the United States using a method perfected by Carothers and his associates. Now it is also manufactured in Russia and in England, by the same method. On polymerization chloroprene gives Neoprene, formerly known as Duprene.

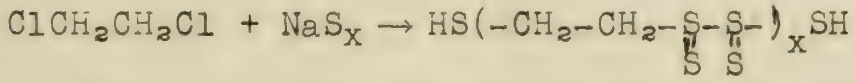
The starting material is acetylene. In the presence of cuprous chloride and ammonium chloride this is polymerized to monovinylacetylene. In the presence of concentrated hydrochloric acid and the above catalysts monovinylacetylene adds HCl:



$$HC\equiv CH \xrightarrow[NH_4Cl]{HCl \atop CuCl} CH_2-\overset{Cl}{\overset{|}{C}}=C=CH_2 \rightarrow CH_2=CH-\overset{Cl}{\overset{|}{C}}=CH_2$$

3. Organic Polysulfides

The polysulfides are made by combination of alkali or of alkaline earth sulfides at about 100°C. Example:



$$ClCH_2CH_2Cl + NaS_x \rightarrow HS(-CH_2-CH_2-\underset{\overset{\|}{S}}{S}-\underset{\overset{\|}{S}}{S}-)_xSH$$

Part of the sulfur in these compounds may be removed by treatment with sodium sulfide, sodium hydroxide, or sulfites:

$$(-RS_4-)_x \rightarrow (-RS_3-)_x \rightarrow (RS_2-)_x$$

(c) [illegible]

[illegible]

(d) [illegible]

[illegible]

[illegible] ed.

1. [illegible] butylene [illegible]

[illegible]

[illegible] of [illegible]

2. [illegible]

[illegible]

[illegible]

3. [illegible]

[illegible]

[illegible]

[illegible]

Properties of the compounds containing fewer atoms of sulfur are said to be much superior. The disulfides may be made directly by oxidation of dimercaptans, following Patrick's method.

$$NaSHCH_2CH_2OCH_2CH_2SHNa \rightarrow (-CH_2CH_2OCH_2CH_2S_2-)_x$$

These organic polysulfides are especially resistant to swelling by oils.

4. Olefines

Simple olefines such as isobutylene are formed in many commercial cracking operations. On polymerization these yield saturated compounds save for one theoretical double bond in the terminal group. Polymerized isobutylenes of molecular weights ranging from 100,000 to 200,000 have been shown by Sparks et al. to have most of the properties of natural rubber. Copolymers with dienes may be formed, allowing vulcanization. These copolymers, of the butyl rubber type, show most of the properties of rubber and have a molecular weight of about 70,000, corresponding to the molecular weight of natural rubber.

Such saturated rubbers are of low specific gravity (less than one), retain their elasticity at low temperatures, resist aging, and are resistant to solvents other than simple hydrocarbons.

Raw material costs and plant construction costs for the production of butyl rubbers are said to be lower than for other artificial rubbers.

A table giving information concerning representative artificial rubbers is appended to this report (page 6).

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Mack, ibid., 56, 2757 (1934).
Meyer, Chem. Ind., 57, 439 (1938).

Reported by Vern McIntosh, Jr.
November 20, 1940

REPRESENTATIVE ARTIFICIAL RUBBERS

Name	Made In	Base Material	Other Materials	Remarks
Buna 85	Germany	Butadiene	None	Polyermized over sodium.
Buna 115	Germany	Butadiene	None	Used only in mixtures. Similar to Buna 85.
Buna N (Perbunan)	Germany	Butadiene	Acrylonitrile	Polymerized in emulsion
Perbunan SP	Germany	Butadiene	Acrylonitrile	Emulsion of Perbunan
Perbunan Extra	Germany	Butadiene	Acrylonitrile	Higher percentage of acrylonitrile. Resists swelling by oil.
Buna S	Germany	Butadiene	Styrene	Polymerized in emulsion. Used on large scale.
SKA	Russia	Butadiene	None	Directly substituted for natural rubber.
SKB	Russia	Butadiene	None	Similar to SKA
Ameripol	U.S.	Butadiene	Present, not named	Apparently polymerized in emulsion. Claimed to be very satisfactory
Neoprene	U. S. England	Chloroprene	None	Resists solvents and chemicals. Heavy.
Sovprene	Russia	Chloroprene	None	Made as in America
Vistanex	U. S.	Isobutylene	None	Behaves like rubber, but may not be vulcanized. Resists conc. acids and alkalies over wide temp.
Oppanol	Germany	Isobutylene	None	Similar to Vistanex.
Butyl Rubber	U. S.	Isobutylene	Dienes	Chemically resistant after vulcanization. Light, strong, perhaps cheap.
Thiokol	U. S.	Ethylene dichloride and sodium polysulfide		Organic polysulfide type. Resists solvents and chem.

REPRESENTATIVE ARTIFICIAL RUBBERS (Cont.)

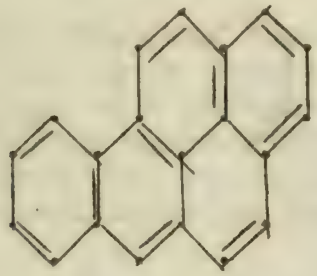
Name	Made In	Base Material	Other Materials	Remarks
Perdurene G.	Germany	Dichlorodiethylether and a polysulfide.		Chemically resistant
Perdurene H	Germany	Dichlordiethylformal		
Perdurene SP	Germany	Dichlordiethylformal		Emulsion of Perdurene H.
Perdurene L	Germany	Dichlordiethylformal		Combination of Perbunan and Perdurene. Chemically resistant.

THE SYNTHESIS OF METHYLCHRYSENES AND RELATED COMPOUNDS

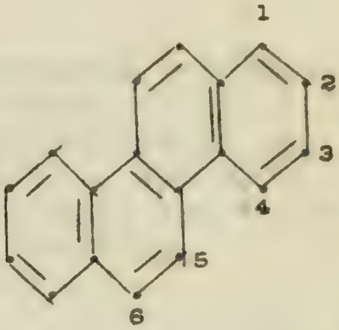
W. E. Bachmann and W. S. Struve

Certain compounds similar in structure to 3,4-benzpyrene (I) are known to exhibit carcinogenic activity, and may be regarded as substituted derivatives of chrysene (II). This report is concerned with the synthesis of several of the six possible monomethylchrysenes.

I



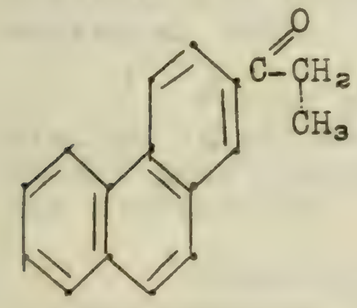
II



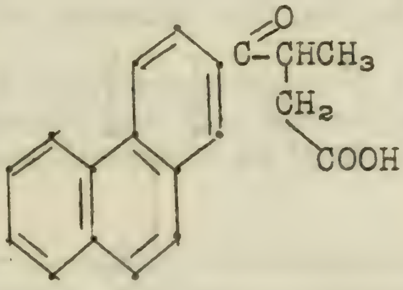
Recently, Bachmann and Struve synthesized 1-methylchrysene and 3-methylchrysens, each by two independent methods, and developed new procedures for obtaining 2-methylcrhysene and 4-methylchrysene. The same men had previously reported preparations of 2-methylchrysene and 4-methylchrysene. The work of certain other investigators in this field will be summarized.

A. Earlier Syntheses of Monomethylchrysenes.

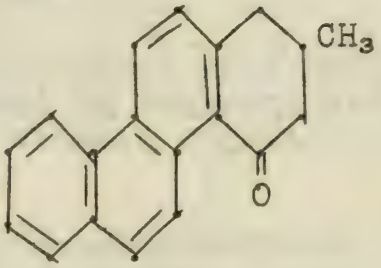
In 1939, Bachmann and Struve used β-(2-phenanthroyl)-butyric acid (IV) as an intermediate in the synthesis of 2-methylchrysene (VI). The acid was made from 2-propionylphenanthrene (III), through a malonic ester synthesis as described by Bachmann and Struve in 1936.



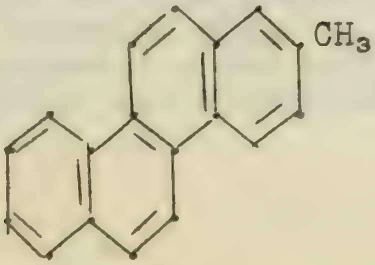
III



IV



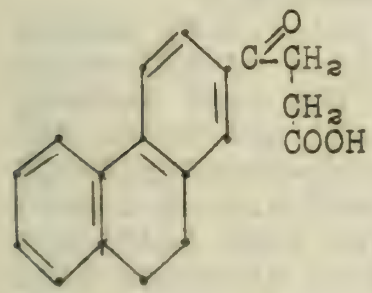
V



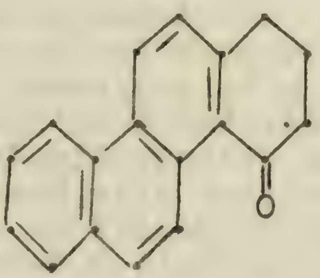
VI

Clemmensen reduction of the acid (IV) yielded α-(2-γ-phenanthryl)-β-methylbutyric acid, which was converted to the acid chloride and cyclized by means of stannic chloride. The 2-methyl-4-keto-1,2,3,4-tetrahydrochrysene (V) was also reduced with zinc amalgam and hydrochloric acid, and the 2-methyl-tetrahydrochrysene formed was readily dehydrogenated to 2-methylchrysene (VI) by palladium on charcoal. The product (VI) crystallized from benzene-alcohol as white leaflets, melting at 229°. A picrate derivative was made which melted at 143°.

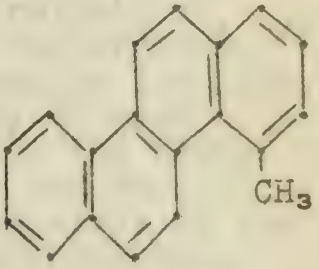
At the same time, the above authors prepared 4-methylchrysene (IX) from 4-keto-1,2,3,4-tetrahydrochrysene (VIII). This cyclic ketone was obtained by reduction and cyclization of β-[2-(9,10-dihydrophenanthroyl)]-propionic acid (VII), which in turn resulted from the reaction between succinic anhydride and 9,10-dihydrophenanthrene as described by Burger and Mosettig.



VII



VIII



IX

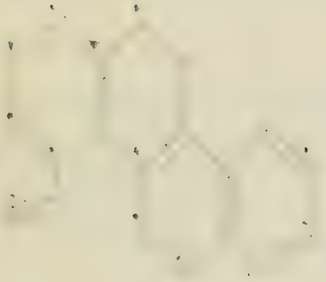
The interaction of methylmagnesiumiodide with the cyclic ketone VIII gave 4-methyl-4-hydroxy-1,2,3,4-tetrahydrochrysene, which could be simultaneously dehydrated and dehydrogenated to yield 4-methylchrysene (IX). When the latter reaction was carried out, using a palladium-charcoal catalyst, the product which was formed crystallized from benzene-petroleum ether as colorless leaflets that melted at 149°. The picrate melted at 134°.

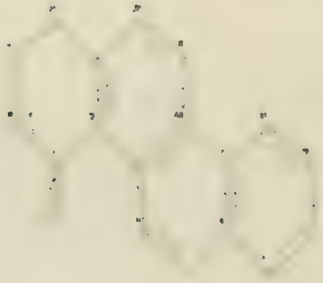
Fieser and Johnson reported a synthesis of 4-methylchrysene similar in all respects to the method used by Bachmann and Struve except that hydrogen fluoride instead of stannic chloride was used in the cyclization.

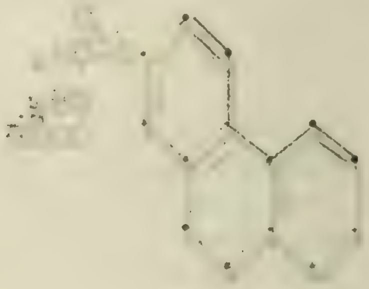
Finally, a lengthy synthesis of 6-methylchrysene (XIII) was accomplished by Newman, wherein α-γ-diphenylbutyric acid (X) was converted to the acid chloride and subjected to an "intra" Friedel-Craft reaction in order to form 1-keto-2-phenyl-1,2,3,4-tetrahydronapthalene (XI) as a starting phase in the synthesis. Originally, benzalacetophenone underwent a 1-4 addition with hydrogen cyanide, and the resulting product was hydrolyzed and reduced to form the acid (X).

Clemmensen reduction of the acid (IV) [illegible] phenanthryl)-γ- [illegible] ylbutyric acid, [illegible] chloride and cyclized by mean[s] of stannic chlori[de] [illegible] 4-keto-1,2,3,4-tetrahy[dro]chrysene (V) [illegible] amalgam and hydrochloric acid, and th[e] [illegible] formed was readily dehydr[ogenated] [illegible] to [illegible] palladium on [char]coal. [illegible] (VI) [illegible] alcohol [illegible] leaflets, [illegible] at 22[illegible] [illegible] was [illegible] It.

[illegible] th[e] [illegible] chrysene [illegible] from [illegible] 2, [illegible] cyclic ke[tone] w[as] [illegible] [2-(9,10-[illegible]hydro[phenanthryl] [illegible] resulted from th[e] [illegible] dihydro[illegible] d[illegible]



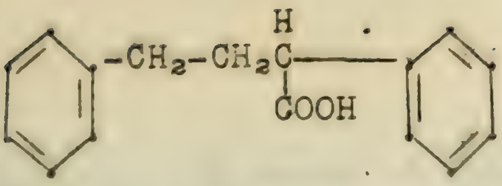




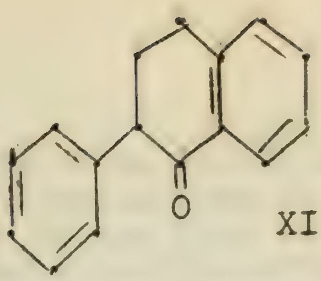
[illegible] th[e] [illegible] to yie[ld] [illegible] out, formed [illegible]

Fi[r]st [illegible] in all re[illegible] that [illegible] the [illegible]ization.

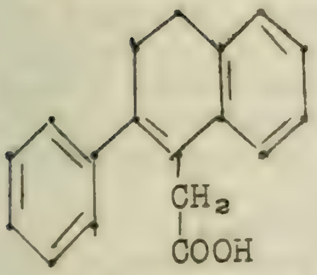
Final[ly] [illegible] accomplished [illegible] converted to [illegible] del- craft [illegible] cycli[zation] [illegible] hydro- napt[h]alene [illegible] [fin]ally, be[illegible] [illegible] [chlo]ride, [illegible] the



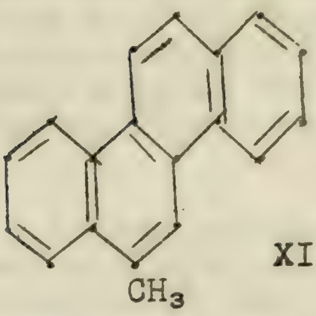
X



XI



XII

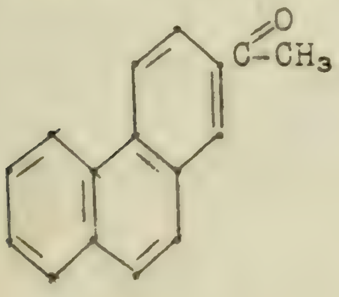


XIII

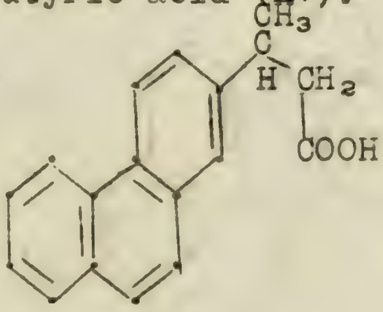
A Reformatsky reaction was employed, using the cyclic ketone (XI), zinc and ethyl bromacetate. After hydrolysis in hydrochloric acid, the product was dehydrated at a temperature greater than 200° with the formation of a double bond in the ring. The ester was then hydrolyzed in potassium hydroxide to give 3,4-dihydro-2-phenyl-1-naphthaleneacetic acid (XII). The newly formed double bond was reduced with sodium amalgam, and the resulting acid was cyclized by action of aluminum chloride on the acid chloride to give 6-keto-5,6,11,12,13,14-hexahydrochrysene. This cyclic ketone was converted to the carbinol by the Grignard reagent, and 6-methylchrysene (XIII) was obtained by dehydration and dehydrogenation. The latter melted at 160°, and its picrate melted at 170°.

B. Recent Syntheses of Monomethylchrysenes

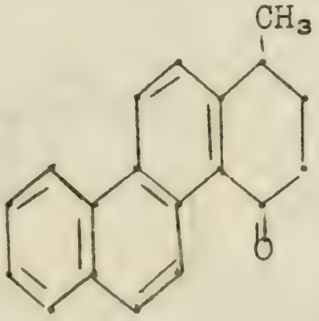
The first independent synthesis of 1-methylchrysene (XVII) involved the use of 2-acetylphenanthrene (XIV) as the starting material. Reduction of the carbonyl group with aluminum isopropylate gave the carbinol, which was converted to the corresponding bromide by means of phosphorous tribromide. This in turn was condensed with sodio-malonic ester, and the product was converted into β-(2-phenanthryl)-butyric acid (XV).



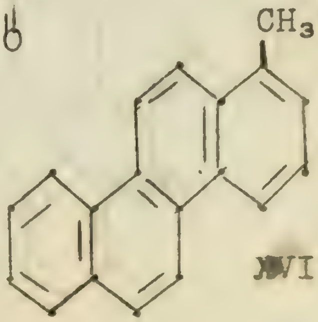
XIV



XV



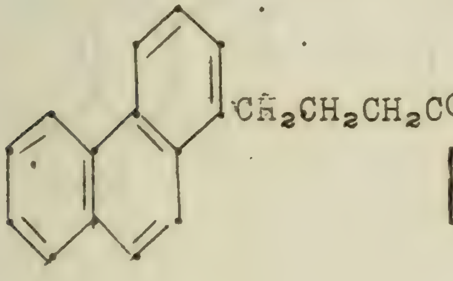
XVI



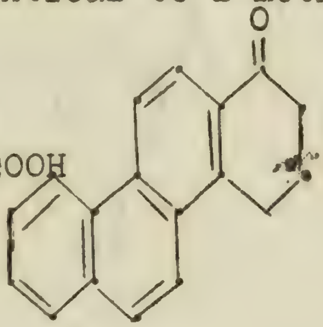
XVII

By means of the Arndt-Eistert reaction, the side chain of the acid (XV) was lengthened so that γ-(2-phenanthryl)-valeric acid was produced, which in turn was cyclized in the form of the acid chloride to give 1-methyl-4-keto-1,2,3,4-tetrahydrochrysene (XVI). A Clemmensen reduction, followed by dehydrogenation over palladium on charcoal, produced a hydrocarbon melting at 249° which was different in character than 5-methyl-1,2-benzanthracene, which would have resulted from a cyclization occurring in the 3 position of the phenanthrene nucleus. The hydrocarbon formed was 1-methylchrysene.

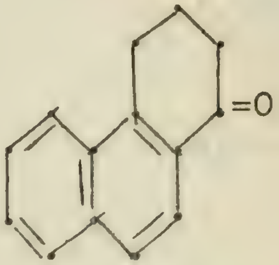
Further proof was furnished by a second synthesis, in which γ-(1-phenanthryl)-butyric acid (XVIII) was cyclized in the form of the acid chloride to 1-keto-1,2,3,4-tetrahydrochrysene (XIX). This ketone (XIX), when converted to the carbinol and then dehydrogenated, yielded a product identical to 1-methylchrysene as obtained above.



XVIII



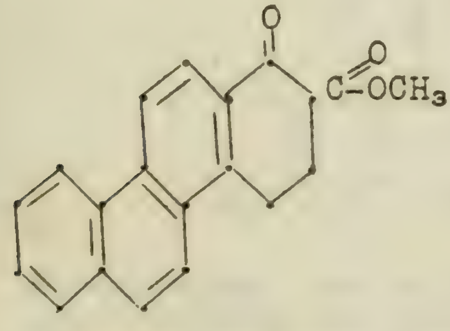
XIX



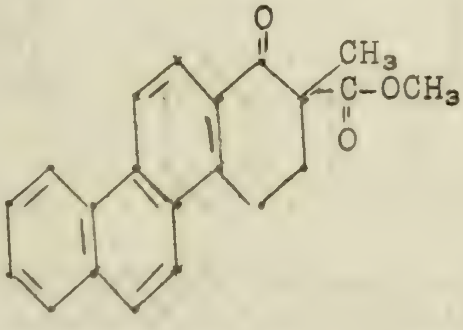
XX

To prepare the acid (XVIII), Bachmann and Struve lengthened the side chain of β-(1-phenanthryl)-propionic acid by means of the Arndt-Eistert reaction, whereas Hoch had previously obtained the identical compound through a different route, using 1-keto-1,2,3,4-tetrahydrophenanthrene (XX) as the starting material.

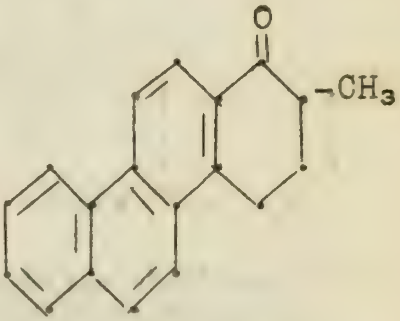
A different type of synthesis was used in getting 2-methylchrysene (VI). Compound (XIX), obtained above, was condensed with methyl oxalate, and the product lost carbon monoxide when heated in the presence of soft glass.



XXI



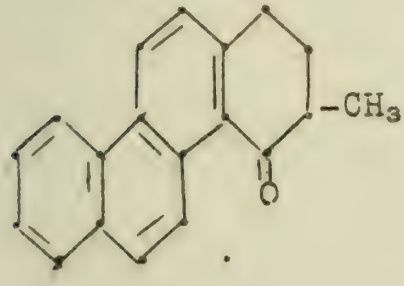
XXII



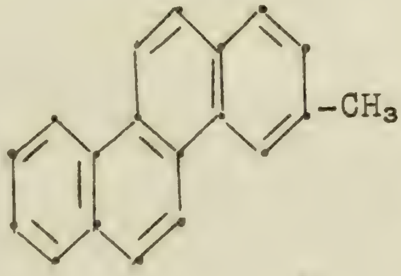
XXIII

The 1-keto-2-carbomethoxy-1,2,3,4-tetrahydrochrysene (XXI) thus formed was converted to 1-keto-2-methyl-2-carbomethoxy-1,2,3,4-tetrahydrochrysene (XXII) through the sodio derivative. Subsequent hydrolysis, decarboxylation, reduction and dehydrogenation gave 2-methylchrysene (VI) which proved to be identical with that obtained previously.

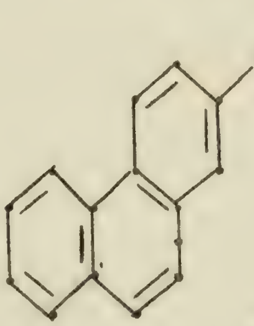
In an analogous manner, 4-keto-1,2,3,4-tetrahydrochrysene (VIII) was used in preparing 3-methylchrysene (XXV).. The intermediate, 3-methyl-4-keto-1,2,3,4-tetrahydrochrysene (XXIV) was also obtained from ω-bromo-2-acetylphenanthrene (XXV) through condensation with sodio-malonic ester and subsequent decarboxylation and cyclization of the acid chloride (XXVII).



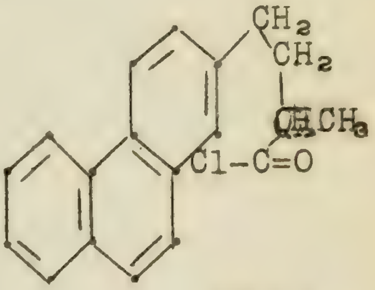
XXIV



XXV



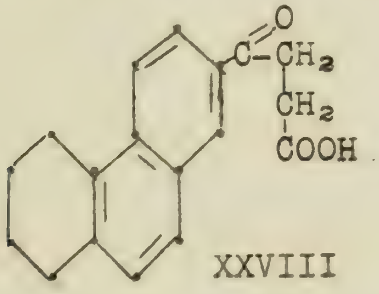
XXVI



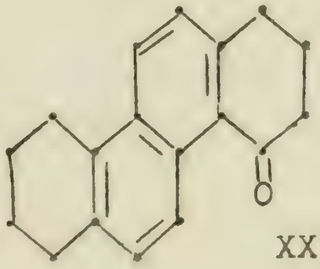
XXVII

The two methods gave the identical ketone (XXIV), which was readily reduced and dehydrogenated to 3-methylchrysene (XXV). This hydrocarbon melted at 170° and its picrate melted at 164°.

Finally, Bachmann and Struve isolated β-[7-(1,2,3,4-tetrahydrophenanthroyl)]-propionic acid (XXVIII) from a reaction between succinnic anhydride and tetrahydrophenanthrene. Its structure was established by reduction and dehydrogenation to the known γ-(2-phenanthryl)-butyric acid.



XXVIII



XXIX

Furthermore, the acid (XXVIII) was reduced and cyclized through its acid chloride to give 4-keto-1,2,3,4,7,8,9,10-octahydrochrysene XXIX, which when treated as previously described, formed the known 4-methylchrysene (IX). The melting points and derivatives proved them to be identical.

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* Main reference

Reported by James A. Robertson
November 27, 1940

THE ERGOT ALKALOIDS

The following alkaloids have been obtained from ergot:

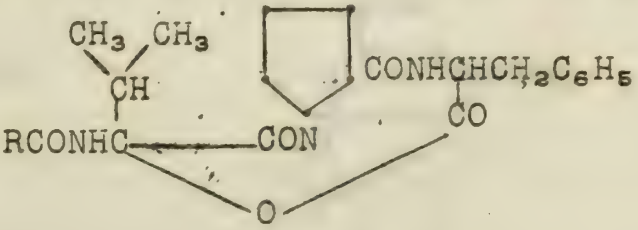
Alkaloid	$[\alpha]_D$ Chloroform	Analysis	Components of side chain
ergotoxine	-197	$C_{35}H_{39}O_5N_5$	α-hydroxyvaline, d-proline l-phenylalanine
erogotinine	+365		
ergocristine	-186	$C_{35}H_{39}O_5N_5$	
ergocristinine	+365		
ergotamine	-155	$C_{33}H_{35}O_5N_5$	α-hydroxyalanine, d-proline, l-phenylalanine
ergotaminine	+385		
ergosine	-161	$C_{30}H_{37}O_5N_5$	α-hydroxyalanine, d-proline, l-leucine
ergosinine	+420		
ergometrine	- 44	$C_{19}H_{23}O_2N_3$	d-2-aminopropanol-1
ergometrinine	+414		

They occur in readily interconvertible diastereoisomeric pairs. The levorotatory members have a high physiological activity; the dextrorotatory are apparently inactive.

$$\text{levo. alkaloid} \underset{\text{alcohol}}{\overset{\text{heat-CH}_3\text{OH}}{\underset{\text{H}_3\text{PO}_4}{\rightleftarrows}}} \text{dextro. alkaloid}$$

All have a methyl imino group and one basic nitrogen atom. The Van Slyke determination shows no free amino groups.

In 1932 Smith and Timmis found that ergotoxine, ergotinine, ergotamine, and ergotaminine gave the same substance ergine on treatment with methanolic KOH. Jacobs showed this to be the amide of an acid $C_{16}H_{16}O_2N_2$ which he named lysergic acid. On complete hydrolysis ergotinine yielded lysergic acid, 1 mole of ammonia, isobutyrylformic acid, d-proline, and l-phenylalanine. The most satisfactory explanation is provided by the structure:



The precursor of isobutyrylformic acid is believed to be the unstable α-hydroxyvaline.

Similar side chains are found in the other alkaloid pairs.

Structure of Lysergic Acid

Properties: Optically active $[\alpha]_D^{20°}$ +40 in pyridine, possesses an N-methyl group. Amphoteric but only one nitrogen atom is basic.

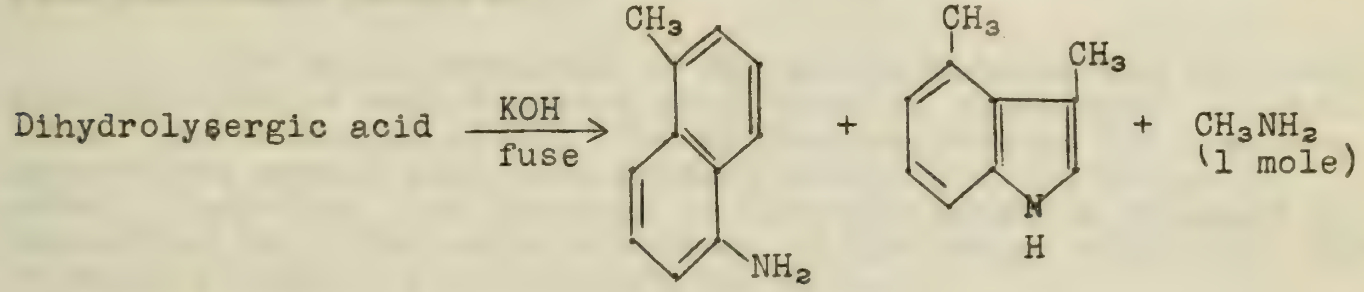
$$\text{lysergic acid} \xrightarrow{200°} CH_3NH_2 \text{ (1 mole)} + CO_2$$

$$\text{lysergic acid} \xrightarrow{CH_2N_2} \text{monomethyl ester}$$

$$\text{lysergic acid} \xrightarrow{\text{reduce}} \text{dihydrolysergic acid}$$

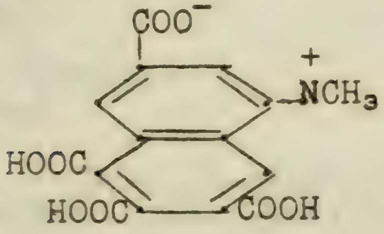
Methyl-dihydrolysergate gives no reaction with acetyl chloride, acetic anhydride, or phenyl isocyanate, but one mole of methane is formed with CH_3MgI.

A characteristic indole odor was noticed when dihydrolysergic acid was fused with KOH. Dihydrolysergic acid, yohimbine, and α,β-dimethylindole have nearly identical ultraviolet absorption spectra, characteristic of the common indole nucleus. The curve for lysergic acid is displaced, indicating a double bond conjugated with the indole nucleus.

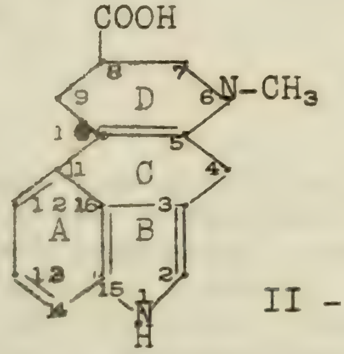


$$\text{lysergic acid} \xrightarrow{HNO_3} \text{tribasic acid } C_{14}H_9O_8N$$

The tribasic acid has an N-methyl group and gives quinoline on distillation with soda-lime. It appears to be an N-methylquinoliumbetainetricarboxylic acid (I).



I



II - lysergic acid

The positions of the carboxyl and the easily reduced double bond in lysergic acid (II) are not shown by the degradations but were determined as follows:

Dihydrolysergic acid has three asymmetric carbon atoms; four racemic modifications are possible. Actually two dihydrolysergic acids have been obtained:

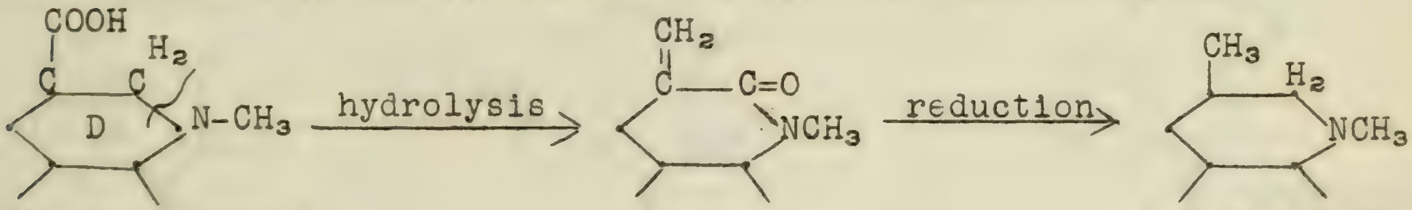
α-dihydrolysergic acid $[\alpha]_D^{25}$ -115 (pyridine)
γ-dihyrdolysergic acid $[\alpha]_D^{25}$ + 32 (pyridine)

Lysergic acid gives on catalytic reduction both forms. Methyl lysergate gives only the α form on reduction and saponification. Similarly the dextrorotatory and levorotatory alkaloids give the γ and α forms respectively. Methyl lysergate mutarotates from +85° to + 118° in boiling methanol. Smith and Timmis have obtained the isomer of lysergic acid by heating the latter in boiling water. Isolysergic acid has a rotation of +365° in pyridine. It is a stronger base and is less rapidly esterified with diazomethane.

The ready isomerization of the lysergic acids can best be explained by the shifting of the double bond (shown in the [5-10] position in formula II). Since isolysergic acid is the stronger base, the double bond must be further removed from the $CH_3N=$ than it is in lysergic acid. The only possibility for a conjugated double bond so placed is (5-10) for lysergic acid and (10-9) for isolysergic acid.

The basic strengths of dihydroergometrine and synthetic 6-methylergoline were compared with those of ethylamine, alanine ester, and β-alanine ester. The difference between the ergoline derivatives agreed with that between ethylamine and β-alanine ester. Therefore, the carboxyl in lysergic acid was assigned to a β-position (8). (The negative effect of the groups -COOR and -CON= on basic nitrogen is practically the same.)

The preceding assignment of the carboxyl to position 8 was confirmed by the pyrolysis of dihydrolysergic acid.



dihydrolysergic acid

6,8-dimethylergoline

The 6,8-dimethylergoline was optically active and melted at 205-212°. Too little was obtained for a further recrystallization. The synthetic 6,8-dimethylergoline was apparently homogeneous although three asymmetric carbon atoms are present. It melted at 226-227°. A mixed melting point of the optically active and the synthetic material was 205-220°. Such a comparison between an optically active material and an inactive one is not valid. However, Jacobs repeated the pyrolysis using racemic dihydrolysergic acid. The 6,8-dimethylergoline obtained was identical with the synthetic.

Dihydro-lysergic acid [illegible]
four racemic acid [illegible]
lysergic acid [illegible]

[illegible]

Lysergic acid given [illegible] forms. [illegible] only [illegible] saponifi- cation. [illegible] [illegible] ly. [illegible] [illegible] of lysergic acid [illegible] lysergic acid [illegible] [illegible]

[illegible] isation [illegible] bond [illegible] I). [illegible] lysergic acid [illegible] removed from the [illegible] acid. The only possibility [illegible] is (8-10) for lysergic acid [illegible]

[illegible] of dihydroergosti[illegible] with those of [illegible]. The diff[illegible] between [illegible] yl in lysergic acid [illegible] effect [illegible]

[illegible] of the [illegible] dihydr[illegible]

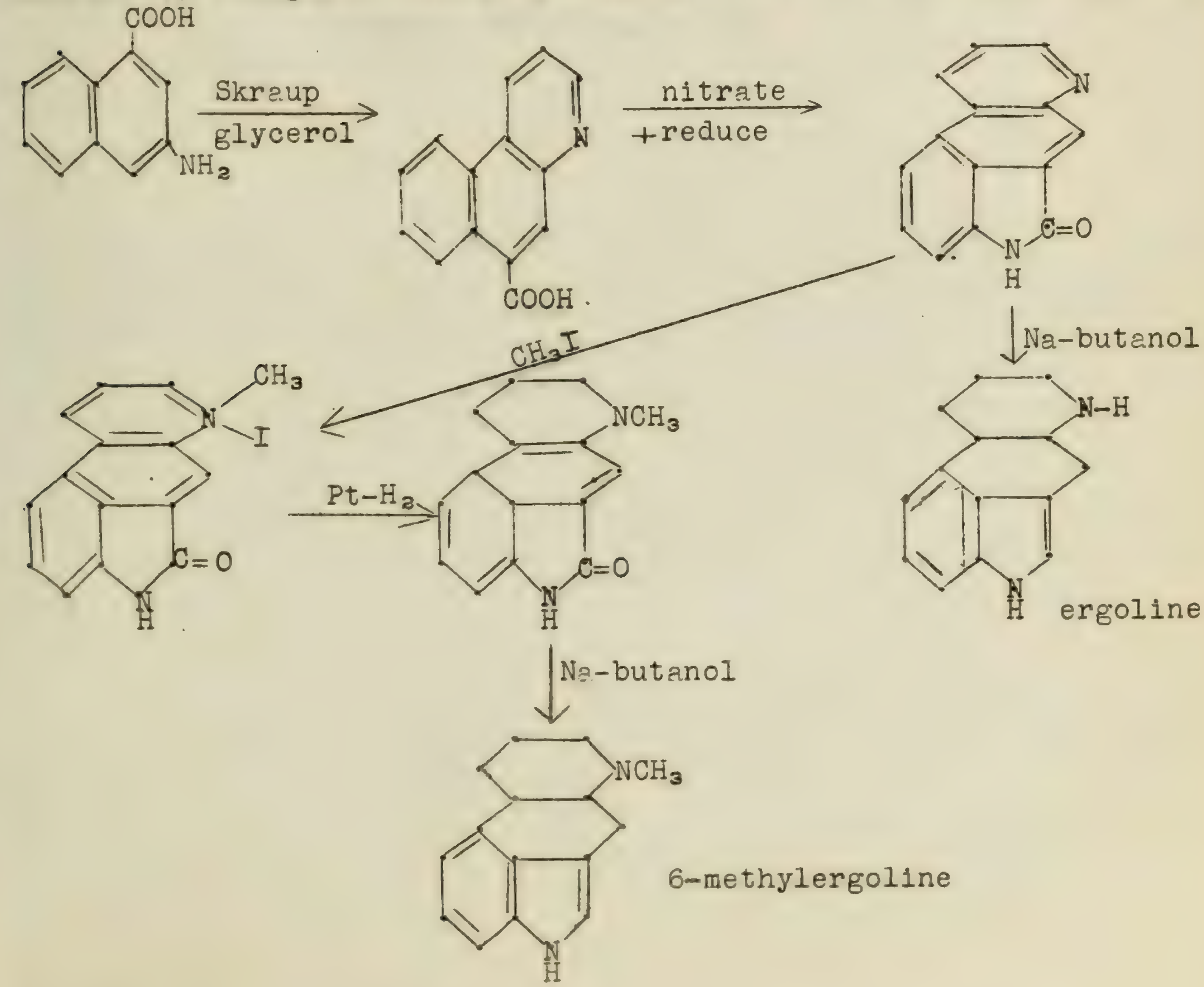
[illegible] line [illegible] obtained [illegible] lized [illegible] oline [illegible] [illegible] ether [illegible]. It melted at [illegible] and the [illegible] [illegible] lysergic acid.

Racemic lysergic acid can be made by heating d-lysergic acid (the naturally occurring form) with barium hydroxide solution at 150°C. or as follows (Stoll):

$$\begin{tikzcd} \text{ergot alkaloids} \arrow[r, "H_2NNH_2"] & \text{racemic isolysergic hydrazide} \arrow[d, "HONO"] \arrow[dl, "KOH"'] \\ \text{racemic lysergic acid} & \text{racemic isolysergic azide} \arrow[d, "NaHCO_3"] \\ & \text{racemic isolysergic acid} \end{tikzcd}$$

Both d- and l-lysergic acids have been obtained through a resolution in which the above azide is condensed with l-nor-ephedrine.

Similarly Stoll has effected a partial synthesis of ergometrine by using d-2-aminopropanol-1 instead of l-nor-ephedrine.



The steps are identical for 6,8-dimethylergoline except that the α,γ-diethyl ether of β-methyl glycerol is used instead of glycerol in the Skraup reaction.

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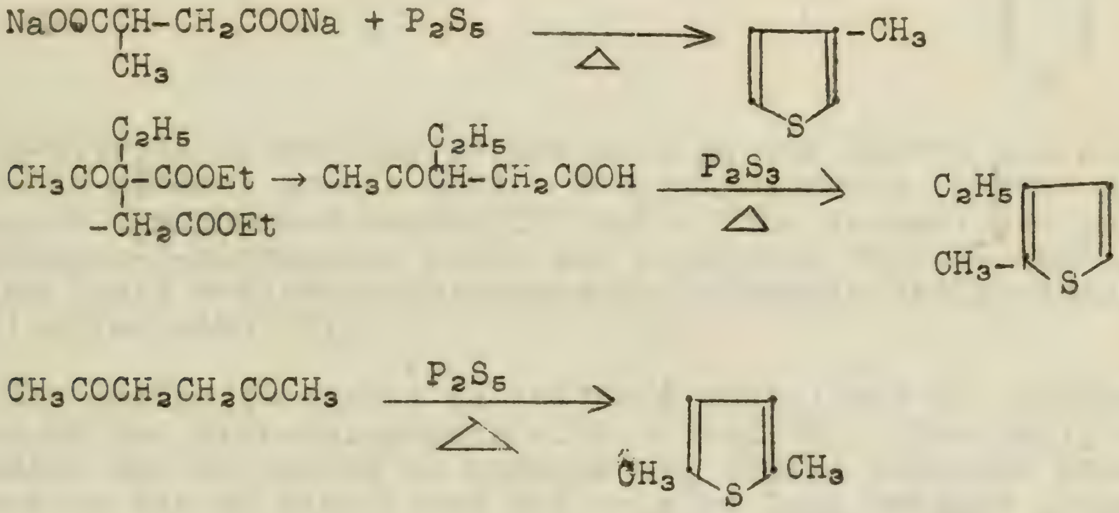
Reported by R. F. Phillips
November 27, 1940

THIOPHENE

Steinkopf et al., Technische Hochschule, Dresden

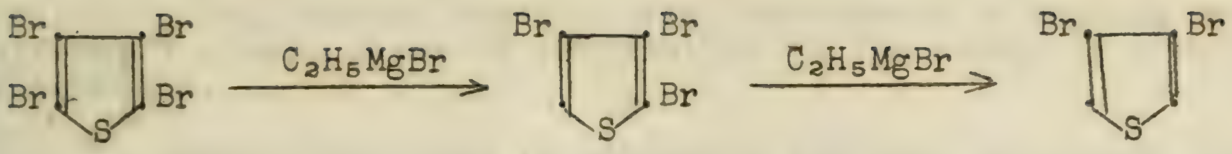
The general chemistry of thiophene resembles that of benzene; with the exception of a few odd reactions (with O_3, gaseous HI, etc.) the difference is only one of degree.

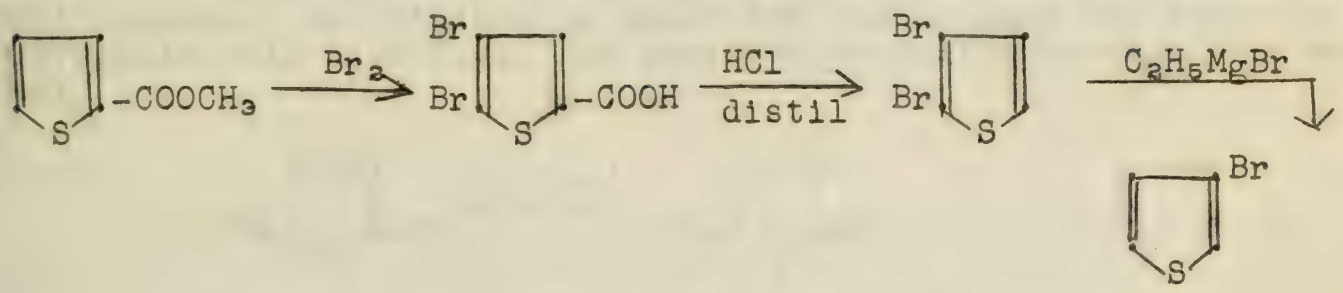
Thiophene is prepared by passing acetylene over pyrites at 300-400° or by treating sodium succinate with P_2S_5. Substituted thiophenes are obtained from substituted succinic acids or in general from 1,4-dicarbonyl compounds with P_2S_5.



The mercuration reaction is important in this series since the poly- or mono-chloromercuri derivatives are easily formed and may be used to characterize the substituted thiophenes. By use of $HgCl_2$ the -HgCl group may be introduced into one or both α positions (depending upon the conditions) or into an active β position if the two α positions are occupied. The fact that the dichloromercuri compound is insoluble in alcohol while the monochloromercuri derivative is soluble facilitates the separation of such isomers as 2-thiotolene (2-methylthiophene) and 3-thiotolene, because the former gives a monomercuri derivative while the latter forms a dimercuri compound. Chloromercuri groups may be introduced into all vacant positions of a thiophene compound by refluxing it with $Hg(OAc)_2$ and treating this mercuri derivative with NaCl. These chloromercuri compounds may be converted into the corresponding iodine substituted thiophenes by action of $KI-I_2$.

Thiophene is halogenated readily to give a mixture of the mono-, di-, tri-, and tetrahalogen compounds. With mild conditions only the α positions are attacked and with the mildest conditions only one α position is substituted. Thus, the 2-bromo-, 2,5-dibromo-, 2,3,5-tribromo-, and the 2,3,4,5-tetrabromo-thiophenes are readily obtained from thiophene or from the corresponding chloromercuri derivative by direct bromination. The synthesis of other substituted bromothiophenes involves removal of the more reactive bromine atoms or blocking of certain positions during the halogenation with subsequent removal of the groups used for blocking.



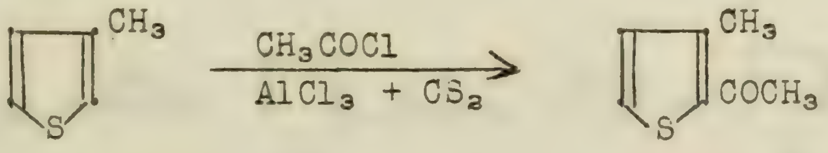


2-Nitrothiophene may be prepared by the direct nitration of thiophene in glacial acetic acid. 3-Nitrothiophene is best made by nitration of thiophene-2-carboxylic acid. The isomeric 4- and 5-nitrothiophene-2-carboxylic acids are separated through the -HgOAc derivative (only 4-nitro-2-thiophene-2-carboxylic decarboxylated by distillation with HCl.

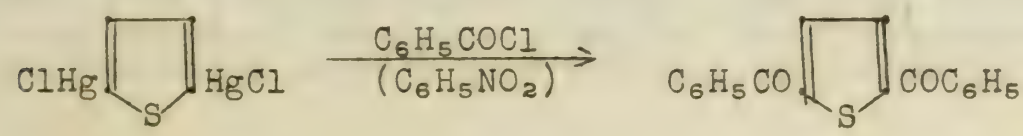
The amines (unstable in the free state) may be obtained by reduction of the nitrothiophenes with Sn and HCl. The $SnCl_4$ complex of the amine may be caused to undergo the Skraup reaction from quinolines or may be diazotized and coupled like primary aromatic amines.

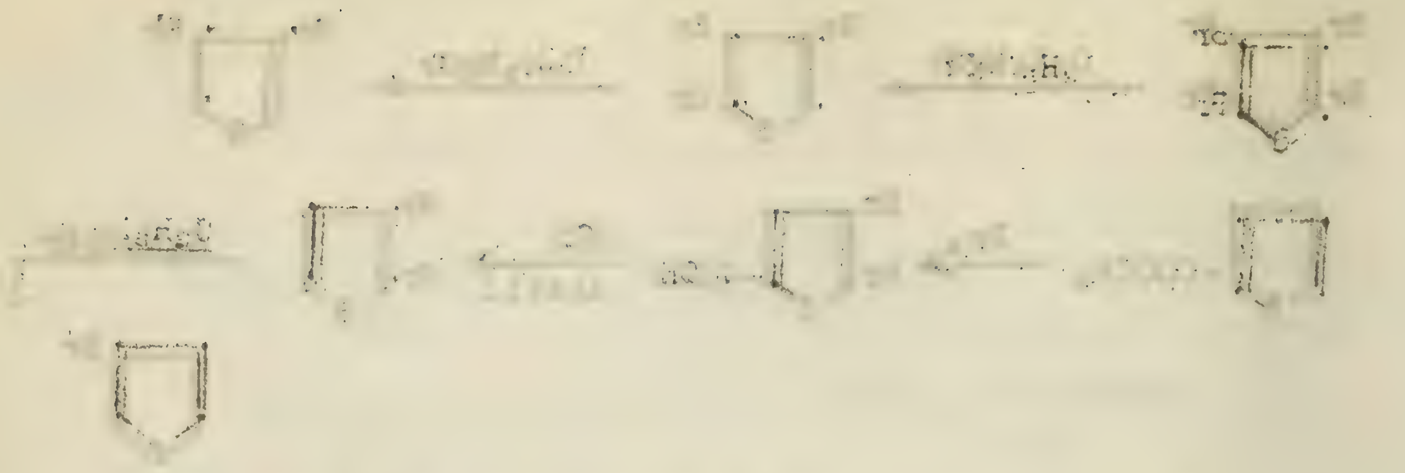
A carboxyl group may be introduced into the thiophene molecule by action of ethyl bromide and magnesium on the bromo- or iodo-thiophene followed by carbon dioxide. Since the thiophene ring is stable to oxidation a methyl or ethyl side chain may be oxidized to the carboxyl group by use of $KMnO_4$.

Thienyl ketones are always prepared through a modified Friedel-Crafts reaction from the acid chloride or anhydride. The reaction proceeds much more readily than in the benzene series as is evidenced by the fact that the $AlCl_3$ may be replaced by P_2O_5, $SnCl_4$, $TiCl_4$, or $HgCl_2$. As usual the α position is attacked the more readily, but if both of the α positions are occupied one of the β carbons is involved.



Chloromercuri groups may be replaced by use of an acid chloride in the following manner:



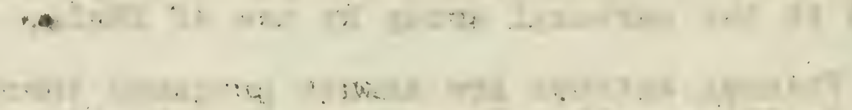


2-alkylthiophenes may be prepared by the direct alkylation of thiophene in [illegible] [illegible] acid. 3-Nitrothiophene is best made by nitration of thiophene-2-carboxylic acid. The isomeric 4- and 5-nitrothiophene-2-carboxylic acids are separated through the [illegible] derivative [illegible] 4-nitro-2-thiophene-2-carboxylic decarboxylated by distillation with HCl.

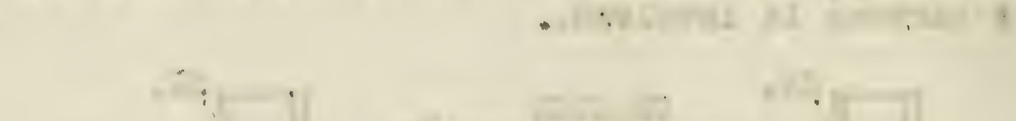
The amines (unstable in the free state) may be obtained by reduction of the nitrothiophenes with Sn and HCl. The SnCl₄ complex of the amine may be heated to undergo the normal reaction from phthalimide or may be diazotized and coupled like primary aromatic amines.

A carbonyl group may be introduced into the thiophene molecule by action of alkyl chloride and [illegible] on the [illegible] thiophene followed by [illegible] [illegible]. Since the thiophene ring is stable to oxidation a methyl or ethyl side chain may be oxidized to the carboxyl group by use of $KMnO_4$.

Thiophene ketones are usually prepared through a modified Friedel-Crafts reaction from the acid chloride or anhydride. The reaction proceeds much more readily than in the benzene series as is evidenced by the fact that the $AlCl_3$ may be replaced by $FeCl_3$, $SnCl_4$, $TiCl_4$, or $HgCl_2$. As usual the 2-position is attacked the more readily, but if both of the 2-positions are occupied one of the 3-carbons is involved.

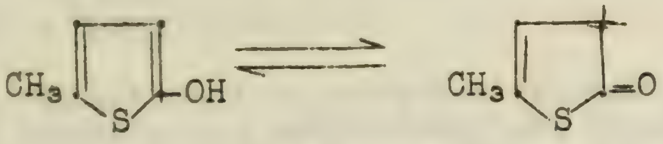


[illegible] groups may be replaced by use of an acid chloride in the following manner:

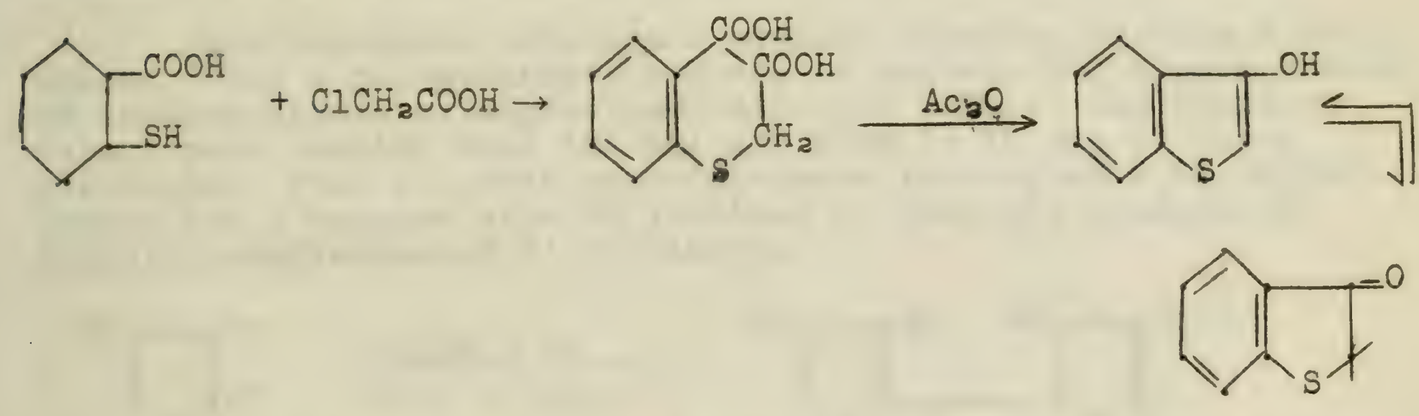


Since these ketones are easily reduced by the Clemmensen reaction, this method together with the direct synthesis (on page 1) affords a simple means of preparation of the isomeric methylethylthiophenes.

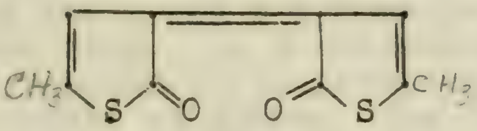
Hydroxythiophene is unknown; however, thiotenol (hydroxymethylthiophene) is obtained in about 20% yields from the reaction of levulinic acid with P_2S_5. An equilibrium exists between the two forms.



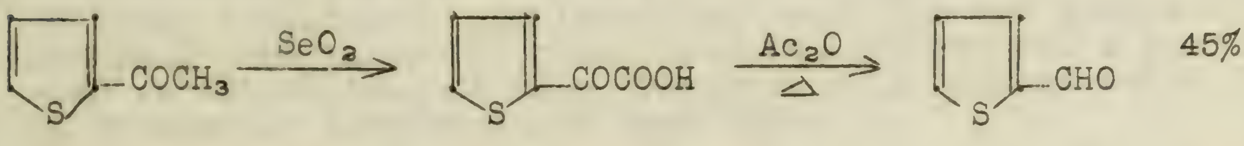
3-Hydroxythionaphthalene also shows this behavior.



These hydroxythiophenes couple with diazonium salts in the position adjacent to the OH. With aldehydes and ketones condensation takes place on the tautomeric keto form. In an alcohol solution with $FeCl_3$ thiotenol condenses with itself to form the simplest indigo known.



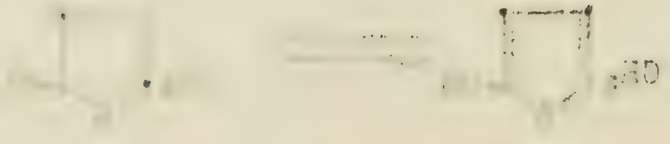
Thiophene aldehydes are very similar to benzaldehyde but somewhat less stable in air. 2-Thiophenealdehyde is obtained in best yields as shown here.



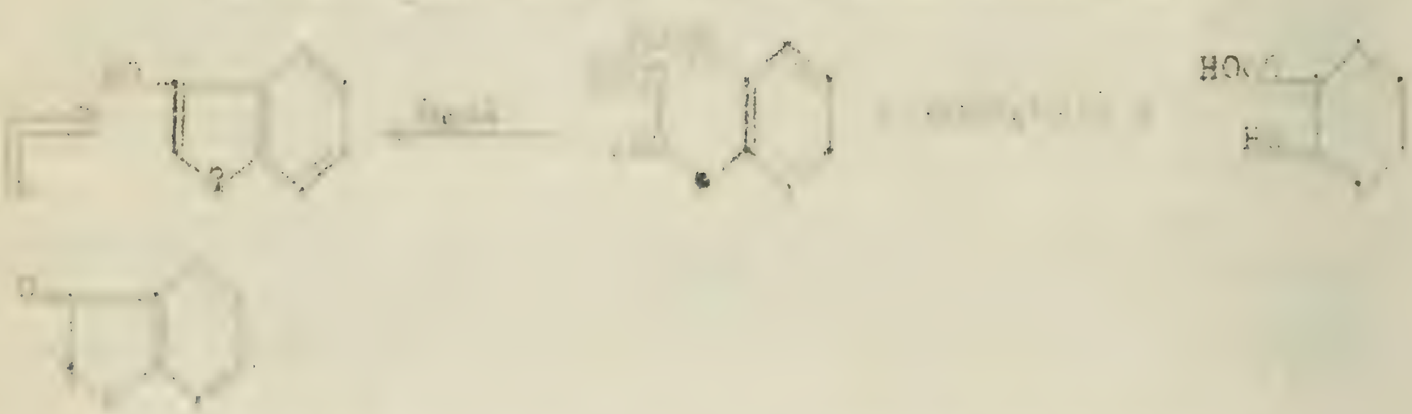
The aldehyde group may be introduced directly using HCN, HCl, and $AlCl_3$ to give about a 10% yield. 3-Thiophenealdehyde has been prepared from 3-thienylmagnesiumiodide and ethyl orthoformate. The only dialdehyde of thiophene known is 3,4-dibromothiophene-2-5-dialdehyde, which is made from 2,5-dimethylthiophene.

Since these systems are easily prepared by the Hinsberg reaction, this method together with the direct synthesis [illegible] page 4 affords a simple means of preparation of the isomeric methylthiophenes.

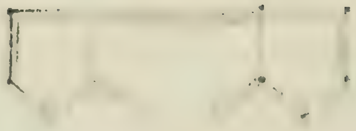
Hydroxythiophenes [illegible] [illegible] [illegible] [illegible] [illegible] methylthiophene [illegible] is obtained [illegible] [illegible] yields from the reaction [illegible] [illegible] [illegible] [illegible]. [illegible] [illegible] between the two forms.



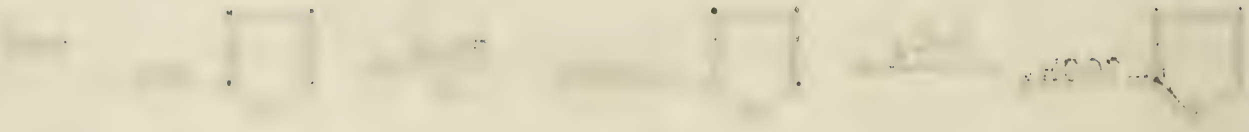
Thioindoxyl [illegible] [illegible] [illegible] [illegible].



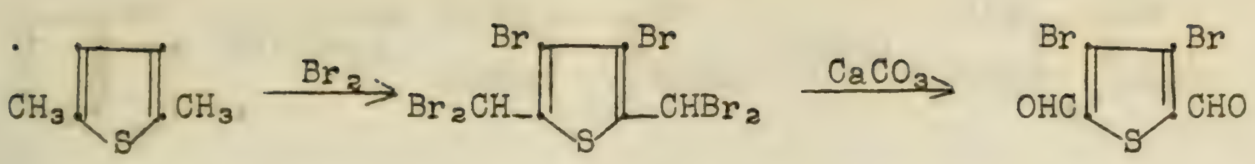
These hydroxythiophenes [illegible] with diazonium salts in the position adjacent to the [illegible]. With aldehydes and ketones [illegible] condensation takes place at the methylene group. In an alcoholic solution with ferric chloride thioindoxyl condenses with itself to form the [illegible] indigo [illegible].



Thiophene aldehydes are very similar to benzaldehyde but somewhat less stable to heat. 2-Thiophenealdehyde is obtained in good yields [illegible] [illegible] [illegible]:



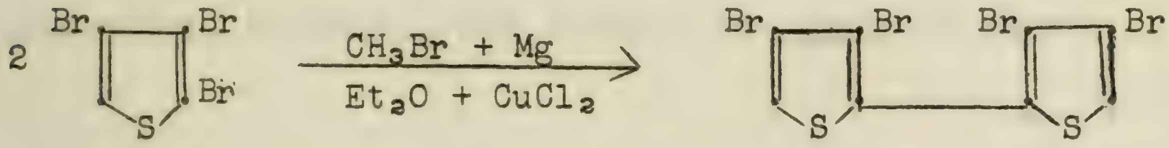
The thiophene group may be introduced [illegible] [illegible] [illegible] [illegible] and $AlCl_3$, to give [illegible] [illegible] [illegible] [illegible]. [illegible] [illegible] [illegible] [illegible] [illegible]. The only difference [illegible] [illegible] [illegible] [illegible] [illegible], which is [illegible] [illegible] [illegible].



This aldehyde is stable under ordinary conditions but it gives an abnormal Cannizzaro reaction in that the aldehyde groups are eliminated. This type of reaction is characteristic of aldehydes having halogen atoms in at least two ortho- positions or an ortho- and a para- position.

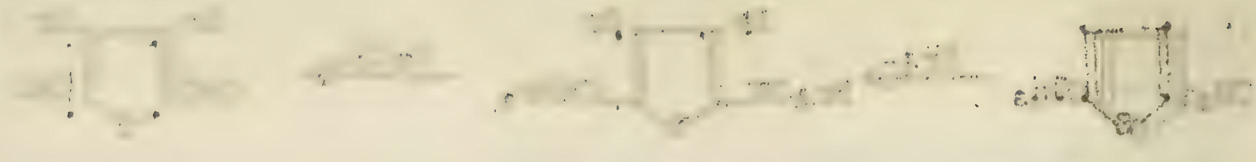
2-Thienylalcohol is prepared in 66% yield from 2-iodothiophene, ethyl bromide and magnesium, and freshly distilled formaldehyde. The action of ClCN on the Grignard reagent from 2-bromothiophene gives 2-thienylcyanide in good yields.

Two thiophene nuclei are coupled together to form a bithienyl when a halogenated thiophene is heated with copper bronze, or treated with ethylmagnesiumbromide and $CuCl_2$. The reaction occurs more readily when the halogen atom is in one of the α positions. When 2,3,4-tribromothiophene is coupled with copper bronze the α bromine atom is involved so that the product is 3,4,3',4'-tetrabromo-2,2'-bithienyl.



All the above reactions have shown the tendency for a reagent to attack one of the α positions of the thiophene molecule. The greater reactivity of the α substituent, especially in the case of the halogen compounds, has been outstanding. However, the reactivities of the α and β hydrogens are conditions by the substituents in the ring. In 2-thiotolene the order of activity of positions with respect to an incoming group is 5>3>4. In 3-thiotolene the order is 2>5>4. The order of reactivity is much the same in the halogenated thiophenes. Ordinarily, the positions adjacent to a nitro or carbonyl group are somewhat deactivated. However, the 3 and 4 positions are not to be regarded as ortho to each other, since the carbonyl group in 2,5-dimethyl-3-acetothienone does not disturb the introduction of a bromine atom into the 4 position. On the other hand, the two groups in 3-methyl-2-carbethoxy-thiophene seem to activate the 4 position to such an extent that on mild treatment with bromine water the atom of bromine is introduced at that point.

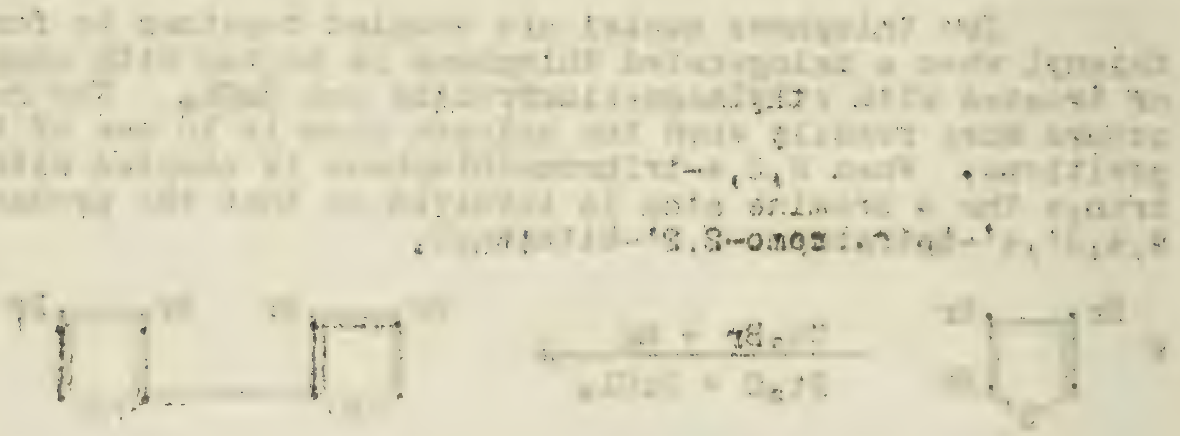
It is interesting to note that an iodine atom in a β position is more reactive than a bromine atom in an α position.



This aldehyde is [illegible] and is given [illegible] when the aldehyde groups are eliminated. This type of reaction is [illegible] of aldehydes having halogen atoms in [illegible] ortho- position or in ortho- and a para- position.

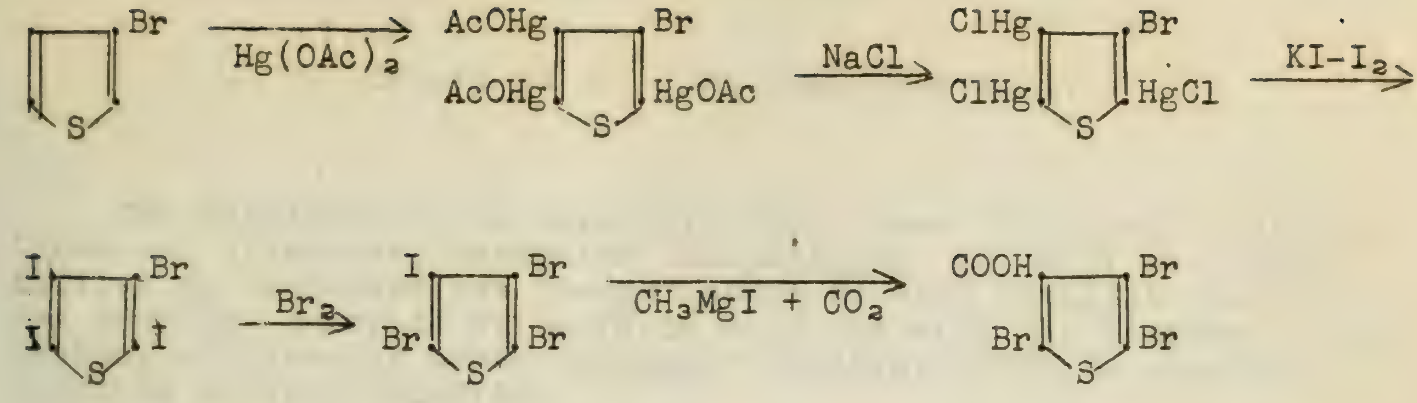
2-[illegible] is prepared in good yield from 2-[illegible], ethyl [illegible] and [illegible]. The action of [illegible] on the [illegible] compound from 2-[illegible] gives 2-[illegible] in good yields.

Two thiophene nuclei are coupled together to form a [illegible] when a halogenated thiophene is heated with copper bronze or treated with [illegible]. The reaction occurs more readily when the halogen atom is in one of the α positions. When 2,4-[illegible]thiophene is [illegible] with copper bronze [illegible] the product is 2,4,2',4'-tetranitro-2,2'-dithienyl.



All the above reactions [illegible] the tendency for a reagent to attack one of the α positions of the thiophene nucleus. The greater reactivity of the α [illegible], especially in the case of the halogen compounds, [illegible]. However, the reactivities of the α and β [illegible] to the substituents in the ring. In [illegible] the order of activity of positions with respect to an [illegible] group is [illegible]. In the thiophene the order is [illegible]. The order of reactivity [illegible] in the halogenated thiophenes. [illegible] adjacent to a [illegible] group [illegible]. However, the 3 and 4 positions [illegible], since the [illegible] group in 2,5-[illegible] into the α position. On the other hand, [illegible] at that point.

It is interesting to note [illegible] 2,3,5-[illegible] position in [illegible] thiophene [illegible] position [illegible].



Once a substituent has been introduced into the thiophene ring it acts the same as the substituent in the benzene ring (when the slight differences in reactivity are overlooked). Because of this it has been comparatively easy to synthesize the thiophene isologs of acridone, fluorenone, dibenzanthracene, etc. In these cases when the benzene ring is replaced with a thiophene ring the color of the compound is always deepened since the thiophene acts as a chromophor.

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Reported by S. P. Rowland
December 4, 1940

REACTIONS OF ALDEHYDES AND KETONES WITH PHENOLS

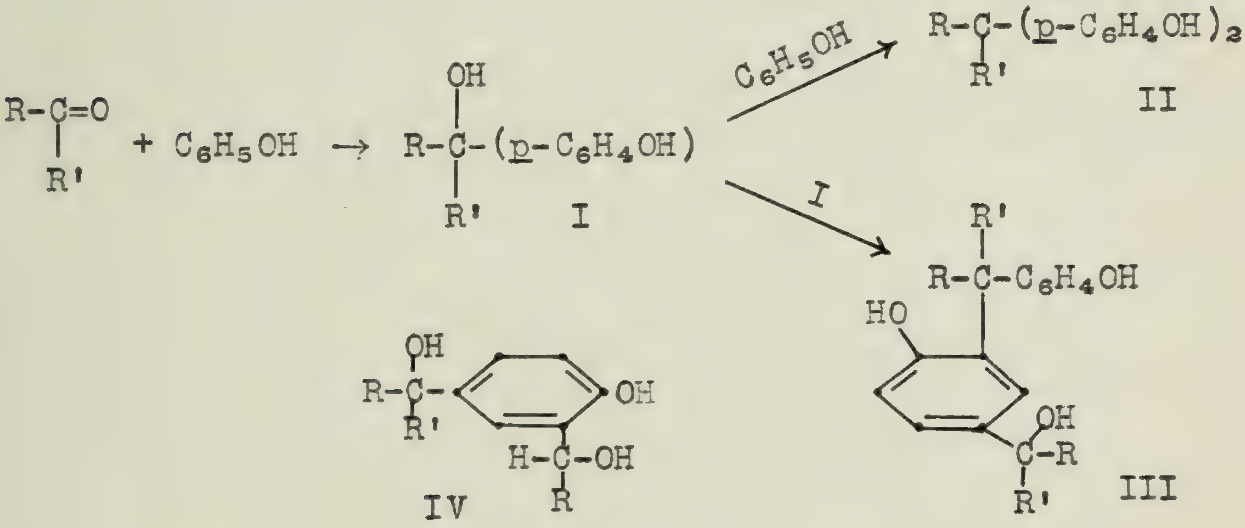
J. B. Niederl et al - New York University

The reactions to be considered are those of phenols with ketones and aldehydes, excepting formaldehyde, and will be further limited to condensations brought about by acid catalysts such as dry hydrogen chloride or sulfuric acid and will not include condensations effected by proton acceptor catalysts such as aluminum chloride or zinc chloride.

Two main types of condensations are encountered: (a) formation of diphenyl methone derivatives, and (b) formation of oxygen heterocycles.

In general, condensations between phenols and ketones differ from those between aldehydes and phenols in the fact that aldehydes tend to form polymers while ketones of all types may form diphenyl methone derivatives which have none of the characteristics of polymers.

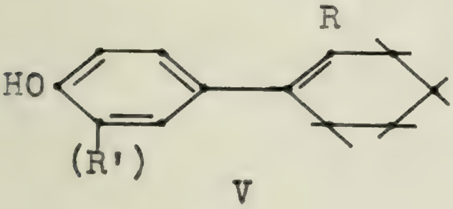
This may be accounted for by the mode of loss of water from the intermediate "phenol-hydrin" (I).



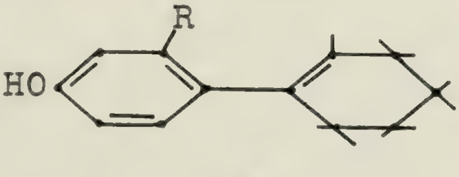
When R' is an alkyl radical, then the predominant reaction is the loss of water with the para hydrogen of another phenol and the diphenyl methone derivative (II) is formed. If R' is hydrogen, then two "phenol-hydrins" may react (III) or the ortho hydrogen may react with another aldehyde (IV). In either case the resulting product is a high-molecular weight polymer. This polymer is formed from most aldehydes in quantitative yields regardless of the conditions employed.

Either of the resulting products when subjected to slow distillation at atmospheric pressure yields the corresponding alkyl phenol. Aldehydes give yields of 20-40% while the ketone derivatives may produce as high as 70% of the alkyl phenol. The position of the entering radical is always para unless this position is blocked. Of commercial interest is the possible production of thymol and dl-menthol from m-cresol and acetone. No pyrolysis experiments with aromatic derivatives are reported but this procedure is possible with alicyclic ketone derivatives.

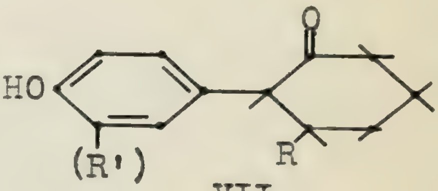
In some cases of steric hindrance, condensation does not proceed further than a "monophenol." Thus if 2-alkylcylcohexanones condense with phenol, compounds of type V are obtained. If the phenol is meta-substituted and the cyclohexanone unhindered, type VI is produced.



V



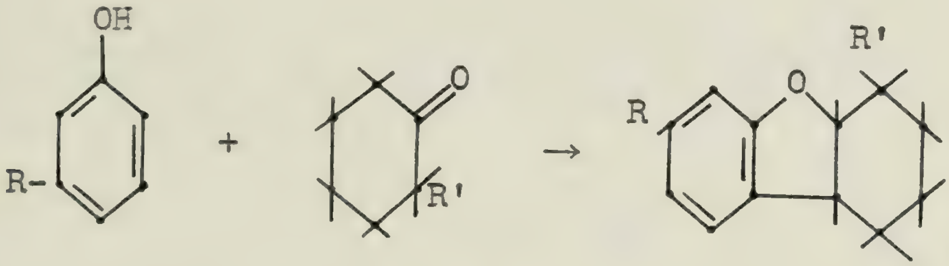
VI



VII

These compounds, when R is methyl, exhibit marked ostrogenic activity. The position of R in compound II is determined by the reactivity of the dibromide. Both bromine atoms are removed by treatment with 0.01 N sodium hydroxide. The pinacol resulting by replacement of bromine atoms by hydroxyl may be rearranged to produce compound VII.

If both reactants are sterically hindered, the condensation is more difficult and yields are lower. The resulting compounds are thought to be coumarans (VIII).

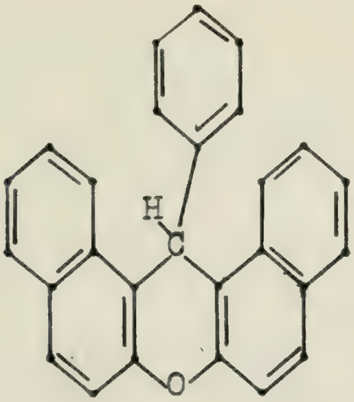


VIII

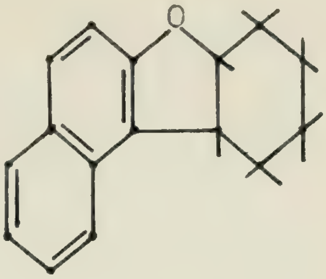
Formation of oxygen heterocycles of type IX has been accomplished by reacting aromatic aldehydes with β-naphthol. In this case the intermediate dinaphthyl methone may be isolated. These compounds are easily oxidized to the corresponding xanthylium salts. β-Naphthol and cyclohexanone produce a benzocoumaran of type Xa or Xb.

The synthesis of benzopyrilium salts may be accomplished by using an α-β unsaturated ketone and resorcinol. This reaction is quite similar to the well-known Skraup synthesis of quinolines.

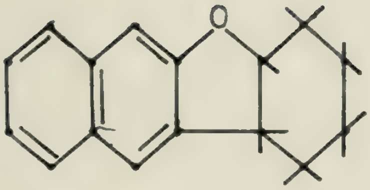
Thus benzalacetophenone and resorcinol react in the presence of HCl and chloranil to give 7-hydroxy-2,4-diphenylbenzopyrilium chloride. This reaction involves the 1-4 addition of the phenol to the double bond system and subsequent removal of water from the intermediate enol XI. The same benzopyrilium salt may be obtained from di-



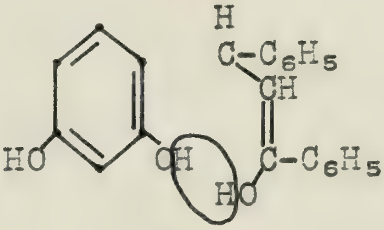
IX



Xa



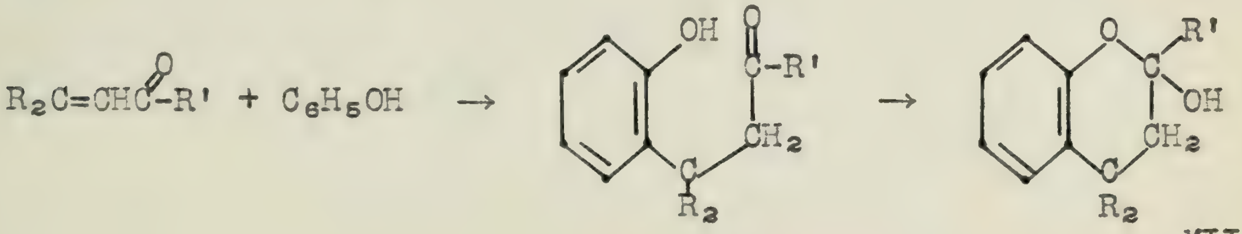
Xb



XI

benzoylmethone.

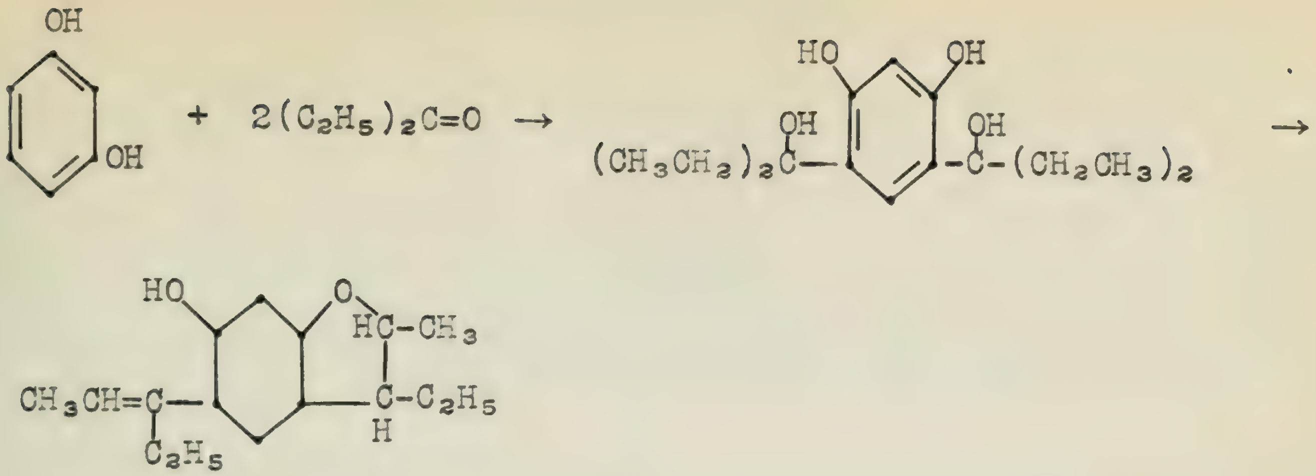
With unsaturated aliphatic ketones, 2-chromanols (XII) and dichromanyl ethers result. The 2-chromanols which are hemiacetals are much less stable than the ethers which are acetals. Both types show the acetal characteristic of being unstable to acid treatment but stable with alkali.



XII

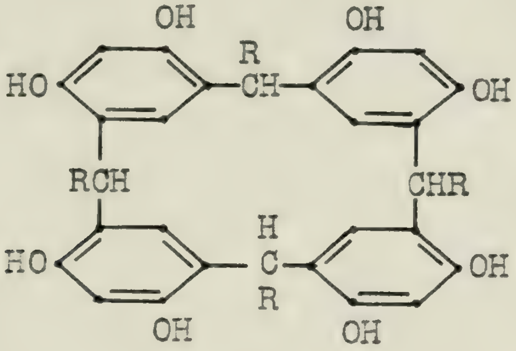
These compounds are insoluble in alkali, lose water to form chromenes on distillation, can be hydrogenated to chromanes oxidatively cleaved to the corresponding β-phenol substituted acid.

Resorcinol may be "multiple alkylated" by treatment with diethyl ketone. The resulting product has been assigned formula XIII.



XIII

With aldehydes, resorcinol is again "multiple alkylated" but equimolar quantities of the aldehyde and resorcinol enter the reaction. The product has eight free hydroxyl groups and is tetrameric. In analogy to the porphins, it has been assigned formula XIV.



R = CH_3, CH_3CH_2, $CH(CH_3)_2$

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Reported by F. J. Wolf
December 4, 1940

THE NITROPARAFFINS
NEW SYNTHETICS FOR SYNTHESIS

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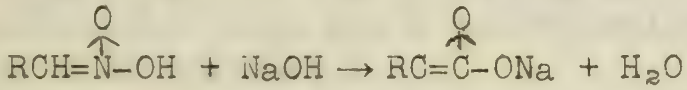
H. B. Hass and Coworkers, Purdue University

The large scale production of the nitroparaffins and some of their derivatives represents a new chapter in the development of the synthetic organic chemical industry. Nitromethane, nitroethane, 1-nitropropane, and 2-nitropropane are now produced commercially by the vapor phase nitration method of Hass. At a later date nitroparaffins with longer carbon chains will be available.

Essentially the nitration process consists of treating the nitroparaffins with nitric acid above the critical temperature of the nitroparaffin, separation of the unreacted portion, and purification of the products. Since all of the products which can be predicted by a free radical mechanism are produced, and no other products have been found, the reaction is believed to proceed through free radicals.

Apparently the nitroparaffins will be utilized chiefly as raw materials for chemical synthesis, but they may become important as solvents, if their price can be lowered. They possess certain specific advantages as solvents for cellulose acetate and vinylites.

In the presence of water nitroparaffins form nitronic acids soluble in strong alkalies:



$$RCH{=}\overset{\overset{O}{\uparrow}}{N}{-}OH + NaOH \rightarrow RC{=}\overset{\overset{O}{\uparrow}}{C}{-}ONa + H_2O$$

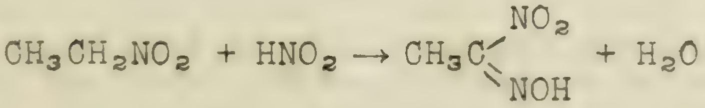
Reduction of nitroparaffins gives the corresponding amines in excellent yields. Meyer showed that by gradual reduction an alkyl hydroxylamine is formed as an intermediate product:

$$CH_3NO_2 \xrightarrow{H_2} CH_3NHOH \xrightarrow{H_2} CH_3NH_2$$

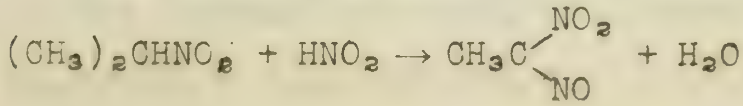
Reduction of the nitroparaffins with stannous chloride yields oximes:

$$CH_3CH_2NO_2 \xrightarrow{SnCl_2} CH_3CH{=}NOH$$

The primary and secondary nitroparaffins react with nitrous acid to form alkyl nitrolic acids and alkyl pseudonitroles, respectively:

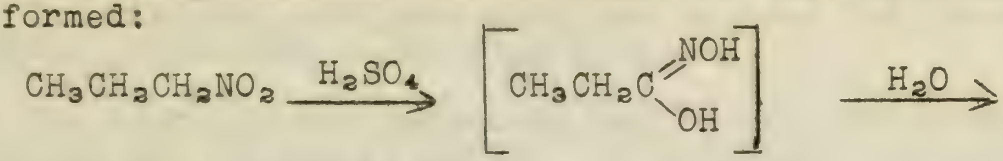


$$CH_3CH_2NO_2 + HNO_2 \rightarrow CH_3C\begin{matrix} \diagup NO_2 \\ \diagdown NOH \end{matrix} + H_2O$$



$$(CH_3)_2CHNO_2 + HNO_2 \rightarrow CH_3C\begin{matrix} \diagup NO_2 \\ \diagdown NO \end{matrix} + H_2O$$

Strong mineral acids in the presence of water convert the primary nitroparaffins into a hydroxylammonium salt of the mineral acid and a fatty acid having the same number of carbon atoms as the nitroparaffins. It is believed that hydroxamic acid is first formed:



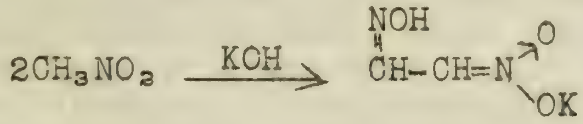
$CH_3CH_2COOH + NH_2OH \cdot H_2SO_4$

When alkali salts of primary and secondary nitroparaffins are added to strong sulfuric acid, the products formed are aldehydes and ketones respectively:

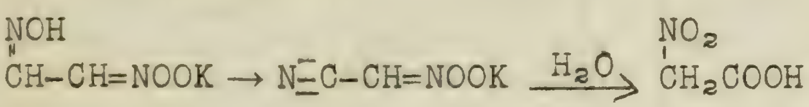
$$CH_3CH{=}NO_2Na \xrightarrow{H_2SO_4} CH_3CHO$$

$$(CH_3)_2C{=}NO_2Na \xrightarrow{H_2SO_4} (CH_3)_2CO$$

Although dilute alkali converts the nitroparaffins to their salts, strong potassium hydroxide reacts with nitromethane to form potassium salt of methazonic acid.



Hydrolysis of the potassium salt of methazonic acid yields nitroacetic acid, which on reduction is converted into aminoacetic acid (glycine):



$$\overset{NOH}{\overset{\|}{CH}}{-}CH{=}NOOK \rightarrow N{\equiv}C{-}CH{=}NOOK \xrightarrow{H_2O} \overset{NO_2}{\overset{|}{CH_2}}COOH$$

The primary and secondary nitroparaffins combine with formaldehyde in the presence of an alkaline condensing agent such as sodium carbonate. The number of moles of formaldehyde which can be combined with a nitroparaffin is equal to the number of hydrogen atoms which are attached to the same carbon as is the nitro group:

$$CH_3NO_2 + 3HCHO \rightarrow (CH_2OH)_3CNO_2$$

Although higher aliphatic aldehydes can also be combined with nitroparaffins, it appears that only one molecule will react, regardless of which nitroparaffin is used.

Reactions of this type are not limited to the aliphatic aldehydes. Aromatic compounds such as benzaldehyde give similar reactions. Nitroethane and benzaldehyde form 1-phenyl-2-nitro-1-propanol and its dehydration product, 1-phenyl-2-nitro-1-propene:

$$C_6H_5CHO + CH_3CH_2NO_2 \rightarrow C_6H_5CHOHCHNO_2CH_3 \rightarrow C_6H_5CH{=}CNO_2CH_3 + H_2O$$

In general, the aldol condensations produce nitrohydroxy compounds in which the hydroxyl radical is attached to a carbon adjacent to the one to which the nitro group is combined. This holds true for the nitroglycols as well as for the nitroalcohols.

Chlorinated aldehydes also can be used for producing nitroalcohols containing a chlorine group.

The nitrohydroxy compounds can be esterified with many of the organic and inorganic acids. On nitration the tris-(hydroxymethyl)-nitromethane reacts similarly to glycerol and forms a trinitrate. This product has been found to be an excellent explosive.

The nitroalcohols can be dehydrated to form nitro olefins. Reaction may be brought about either by treating a nitroalcohol with a dehydrating agent such as zinc chloride or by reacting an ester of the nitroalcohol with sodium carbonate.

$$RCHNO_2CHOHR' \xrightarrow{ZnCl_2} RCNO_2{=}CHR' + H_2O$$

The nitrohydroxy compounds are reduced by hydrogen or other reducing agents to the corresponding aminohydroxy compounds. Thus the tris-(hydroxymethyl)-nitromethane is reduced to tris-(hydroxymethyl)-aminomethane, etc. Aminohydroxy compounds of this nature form organic soaps when mixed with higher fatty acids such as oleic or stearic. These soaps are excellent emulsifying agents. On heating such soaps, amides are formed:

$$RCOOH\text{-}NH_2C(CH_2OH)_3 \rightarrow RCONHC(CH_2OH)_3$$

The aryl alkyl nitroalcohols and nitroolefins react similarly to the aliphatic nitrohydroxy compounds. Thus the 1-phenyl-2-nitro-1-propanol may be reduced to 1-phenyl-2-amino-1-propanol, and 1-phenyl-2-nitro-1-propene to 1-phenyl-2-aminopropane, the salts of which have pharmaceutical uses.

Chloronitroparaffins may be formed by chlorinating the sodium salt of a nitroparaffin. When chlorination is carried out in this way the chlorine attaches itself to the same carbon atom with which the nitro group is combined. Therefore, the number of chlorine atoms which combine with a given nitroparaffin is the same as the number of hydrogen atoms attached to the carbon bearing the nitro group.

The product produced by the complete chlorination of nitromethane in the presence of calcium carbonate or from the alkali salt is know as chloropicrin, which is reacted with sodium ethylate to produce ethyl orthocarbonate and with ammonia to produce guanidine:

$$CCl_3NO_2 + 4NaOC_2H_5 \rightarrow (C_2H_5O)_4C + NaNO_2 + 3NaCl$$

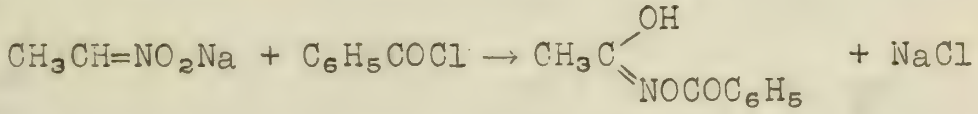
$$CCl_3NO_2 + NH_3 \rightarrow HN{=}C(NH_2)_2$$

Miscellaneous reactions:

The potassium salt of nitroethane combines with diazobenzene nitrate to yield nitroacetaldehyde phenylhydrazone:

$CH_3C(NO_2)=N-NH-C_6H_5$

If reacted with benzoyl chloride, alkali salts of nitroethane yield benzoyl acetohydroxamic acid:



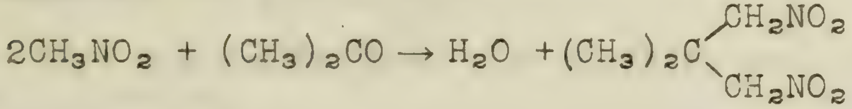
$$CH_3CH=NO_2Na + C_6H_5COCl \rightarrow CH_3C\begin{matrix}\diagup OH \\ \diagdown NOCOC_6H_5\end{matrix} + NaCl$$

The reaction between nitroethane and ethylzinc results in the formation of β-ethyl-β-*sec*-butyl hydroxylamine.

Mercury fulminate is the product obtained when mercuric chloride and sodium nitromethane are reacted together:

$$2CH_2=NO_2Na + HgCl_2 \rightarrow (C=NO)_2Hg + 2H_2O + 2NaCl$$

Nitromethane can be condensed with ketones to yield dinitro compounds:



$$2CH_3NO_2 + (CH_3)_2CO \rightarrow H_2O + (CH_3)_2C\begin{matrix}\diagup CH_2NO_2 \\ \diagdown CH_2NO_2\end{matrix}$$

Dinitro compounds can also be produced by treating a chloronitroparaffin with the sodium salt of a nitroparaffin:

$$CH_2NO_2Na + CH_3CHClNO_2 \rightarrow CH_3CHNO_2CH_2NO_2 + NaCl$$

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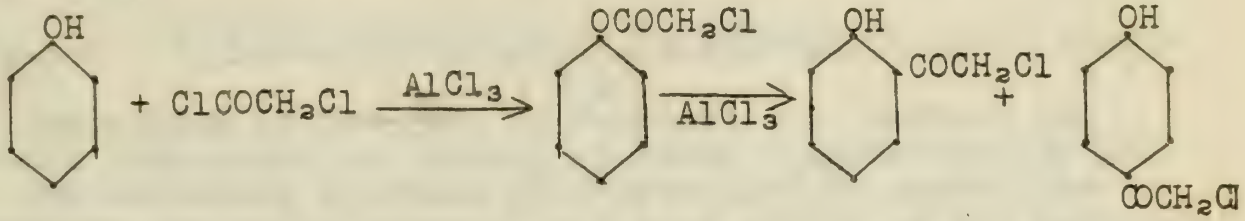
Reported by R. Stephenson
December 11, 1940

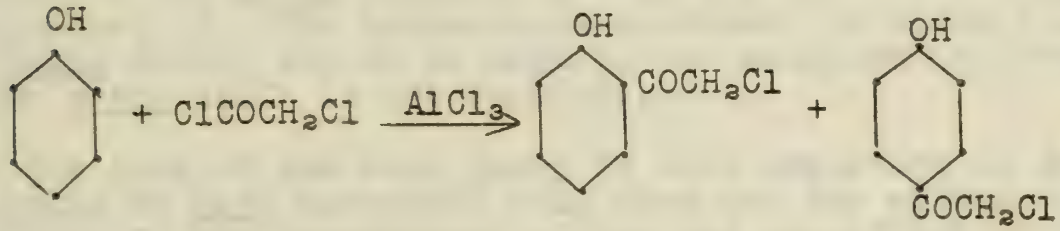
FRIES REARRANGEMENT

The Fries reaction (equation I) is similar to the Friedel-Crafts reaction (equation II) in that the starting and final products are the same in both cases. The difference lies in the formation of an intermediate compound in the Fries reaction.

I



II



Although the Friedel-Craft reaction usually introduces only one substituent, Fries found that reaction II gave a mixture of mono and diketone. It was for this reason that Fries originally used reaction I. The yields by this method are, furthermore, usually much better than by the Friedel-Craft.

The best general methods for carrying out the rearrangement are the following:

1. To obtain the p-hydroxy ketone. A solution of the phenol ester and an equal molar quantity of $AlCl_3$ in nitrobenzene is heated at 60° for one hour or left at room temperature for twenty-four hours.

2. To obtain the o-hydroxy ketone. Heat an intimate mixture of the ester and an equimolar quantity of $AlCl_3$ without a solvent for 20-40 minutes at 140°C.

Modifications of the above procedures consist in replacing $AlCl_3$ by $ZnCl_2$ or BF_3, or consist in using chlorobenzene or tetrachloroethane as a solvent in the rearrangement to the ortho substituted product.

The course of the reaction depends on three factors. These are the temperature of the reaction, the particular type of acyl group, and the particular type of phenol group.

The shift to form the para ketone tends to take place at lower temperatures and the shift to form the ortho group tends to take place at higher temperatures. An interesting illustration is the case of m-cresyl acetate which at 25° rearranges to give 100% p-hydroxy ketone, and at 165° rearranges to give 100% o-hydroxy ketone. At intermediate temperatures, a regular gradation in amounts of ortho and para are formed. It has further been shown that when the para is heated with $AlCl_3$, the o-hydroxy ketone is obtained.

Acyl groups of many types of acids have been used in the rearrangement. According to Rosenmund and Schnurr, the rate at which the shift takes place decreases in approximately the following order -

$CrH_{2n+1}CO(n=1\cdots5) > C_6H_5CH_2CO > C_6H_5CH_2CH_2CO > C_6H_5CH{=}CHCO > C_6H_5CO$

Importance of the rate is twofold: 1. Certain rearrangements take place too slowly at lower temperatures to be useful. The necessary increase in temperature to hasten the shift produces the ortho compound and good yields of the para are not obtainable; 2. The temperature necessary to cause a useful rate of ortho shift, may be so high as to decompose the product and so the ortho shift is not feasible.

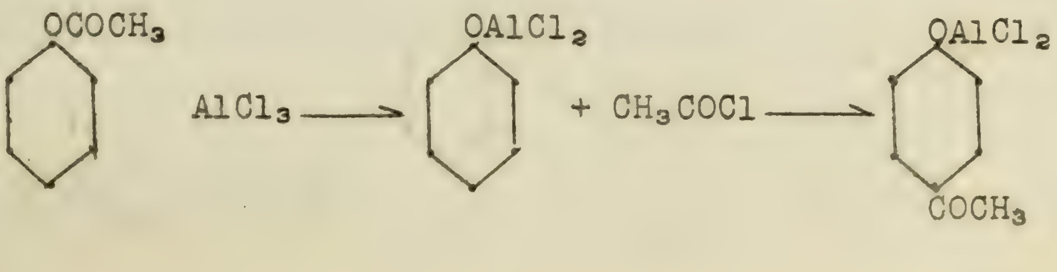
The size of the acyl group is also important in determining whether ortho or para compounds will form but the effect is small in comparison to the temperature effect and the effect of the phenol.

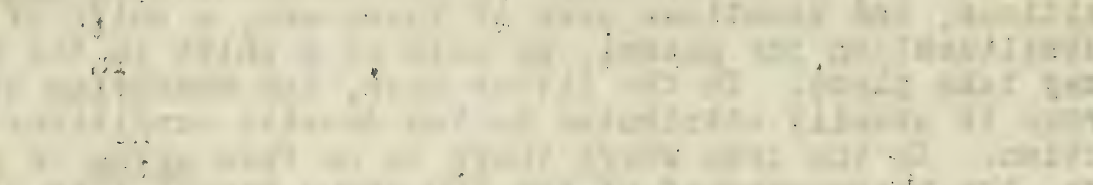
The phenols used have been derived from benzene, naphthalene, phenanthrene, biphenyl and coumarin. Some substituents on the phenol inhibit the rearrangements. Examples are the nitro or benzoyl groups when ortho or para to the ester group, or carboxyl or acetyl groups when para to the ester group. When the phenol is alkyl-substituted as with methyl or ethyl groups, the shift usually takes place as expected provided ortho or para positions are available. If, however, there are no unsubstituted ortho or para positions, and sometimes even if there are, a shift of the alkyl substituent on the phenol, as well as a shift in the RCO group, may take place. In the latter case, the wandering of the alkyl group is usually attributed to too drastic conditions for the reaction. In the case where there is no free ortho or para positions, the rearrangement of the RCO group cannot take place without the shifting of an alkyl group.

Mechanisms - The three mechanisms so far postulated for the Fries reaction, all show possible ways in which the reaction might take place. The proof of each mechanism consists in showing that the reaction can proceed in a given manner. None of the mechanisms, however, eliminate any alternative path, and as yet no mechanism has been shown superior to any other.

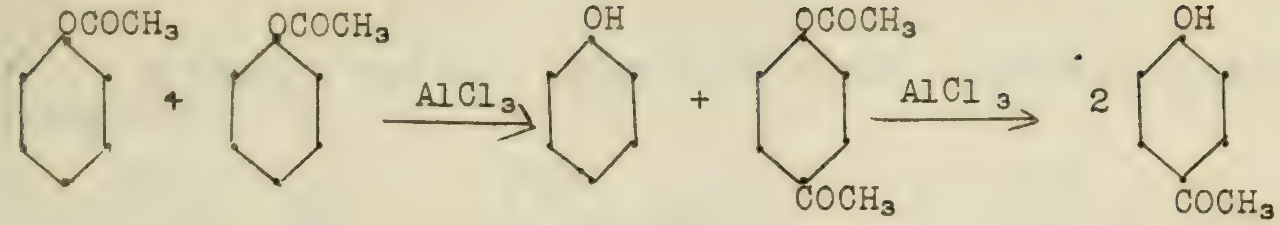
The mechanisms are:

Skraup and Cox -

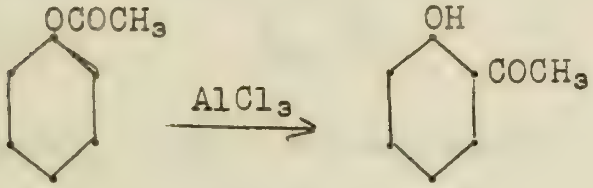




Rosenmund and Schnurr -



Auwers -



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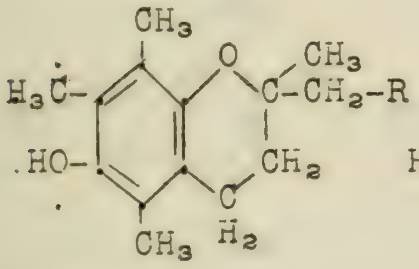
Reported by R. I. Meltzer
December 18, 1940

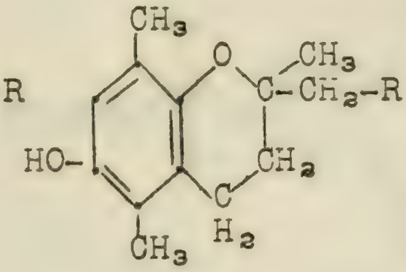
SYNTHESIS OF VITAMIN E AND SIMILAR COMPOUNDS

Lee Irvin Smith University of Minnesota
P. Karrer University of Zurich

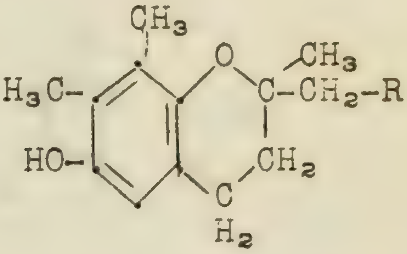
Vitamin E has been shown to be three compounds; α-, β-and γ-tocopherol.



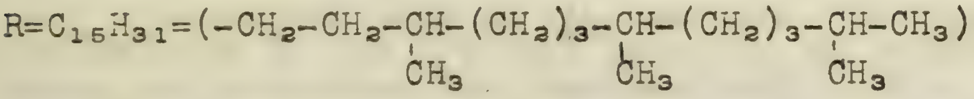
I - α-tocopherol



II - β-tocopherol

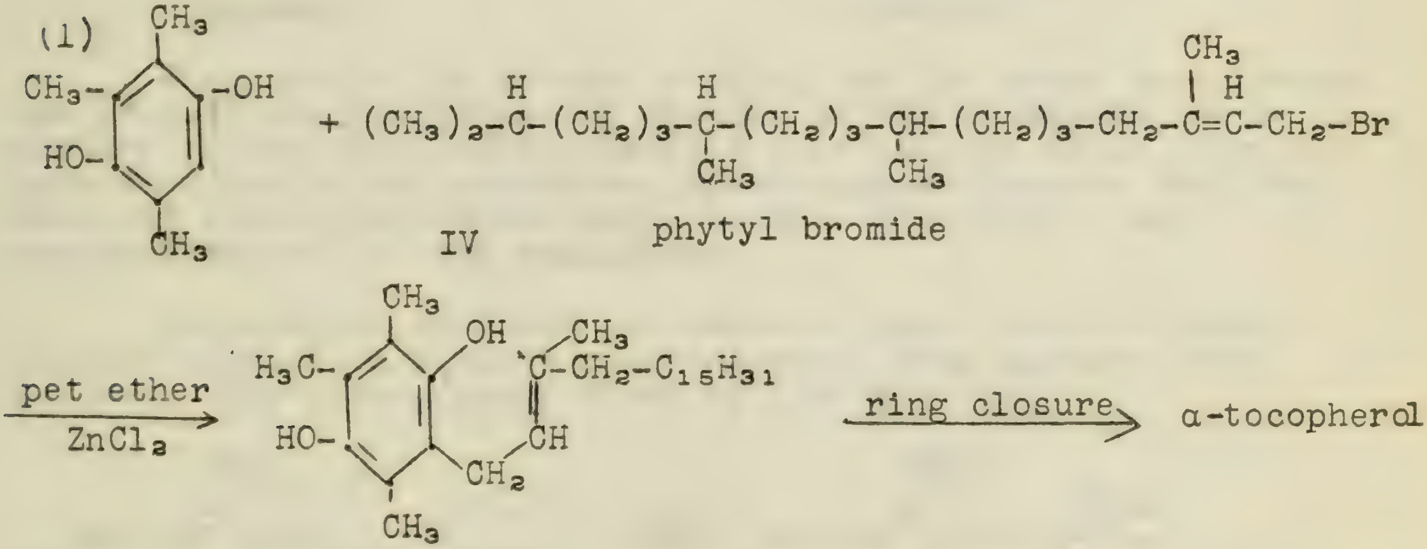


III - γ-tocopherol



$R=C_{15}H_{31}=(-CH_2-CH_2-\underset{CH_3}{CH}-(CH_2)_3-\underset{CH_3}{CH}-(CH_2)_3-\underset{CH_3}{CH}-CH_3)$

β-Tocopherol and γ-tocopherol are isomers, α-tocopherol is a higher homolog. The structures have been proven in each case and the chemical proof has been presented in two previous seminars. The methods used were oxidative degradations and fitting together of the products; and synthetic methods. Finally Karrer synthesized α-tocopherol from tocmethyl hydroquinone and phytyl bromide, establishing the structure.

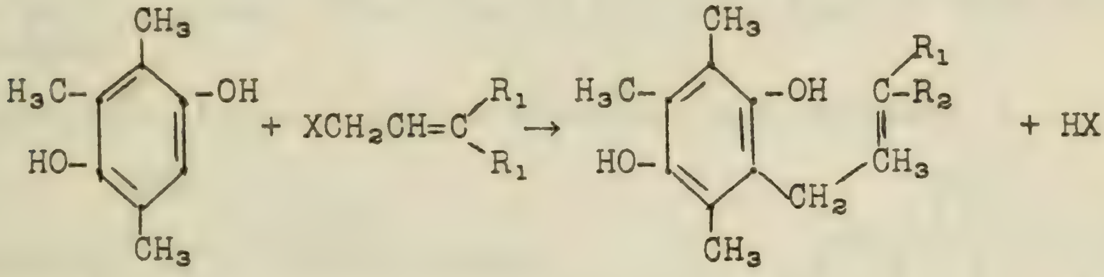


Synthesis of Compounds similar to Vitamin E

The synthesis of chromans resembling Vitamin E is often rather simple. The starting materials are hydroquinones or phenols having vacant one position in the ring ortho to the OH group. These are condensed with allylic halides or alcohols, or with conjugated dienes. Frequently the reaction proceeds so

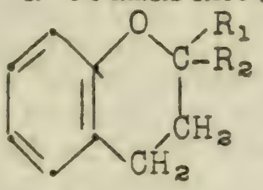
smoothly that neither solvent nor catalyst is required, especially when allylic halides are used. In the case of allylic alcohols, an inert solvent such as petroleum ether or benzene is used, with $ZnCl_2$ as catalyst. For the dienes, acetic acid is used as the solvent, with dry HCl as catalyst.

(2)

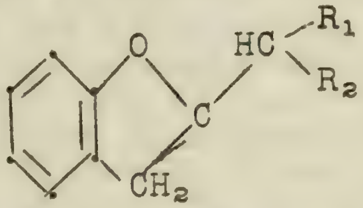


X = OH or halogen

The second step in the reaction, the ring closure, involves the addition of the hydroxyl group to the double bond in the side chain, in accordance with Markownikoff's rule. If R_1 and R_2 are both alkyl, a chromane is obtained, while if these groups are both H, addition will occur in the reverse manner and the product will be a coumarane.



chromane

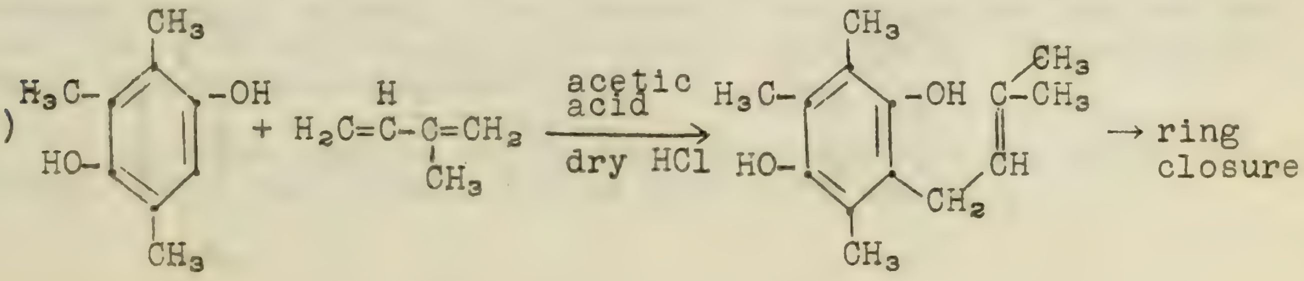


coumarane

When one of the groups is alkyl and the other is hydrogen, the product may be either the chroman or the coumarane, or a mixture of the two. Markownikoff's rule applies fully since the nature of one of the reactants (hydroquinone) insures that the reaction takes place under anti-oxidant conditions. Any peroxide effect is thus negligible.

The allylic alcohols and halides react first by direct nuclear allylation without rearrangement; ring closure then follows. The dienes react first by 1,4 addition.

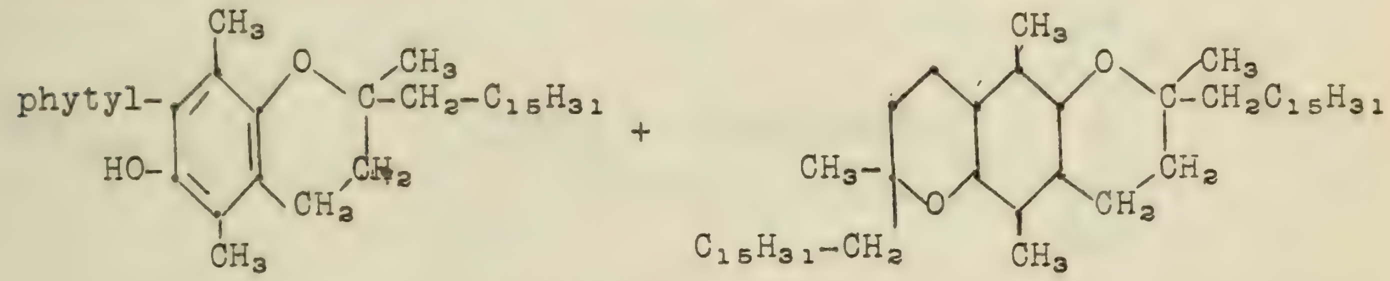
(3)



Synthesis of β- and γ-Tocopherols

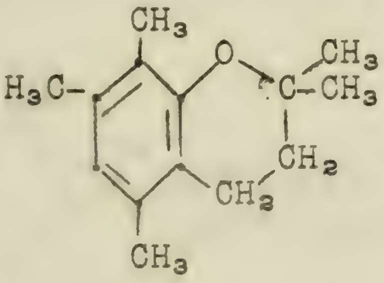
The great reactivity of allylic compounds coupled with the enhanced reactivity of the aromatic nucleus, due to the presence of the methyl groups, leads to the easy introduction of more than one phytyl group, resulting in the formation of complicated mixtures.

pxylohydroquinone + phytyl bromide → β-tocopherol +



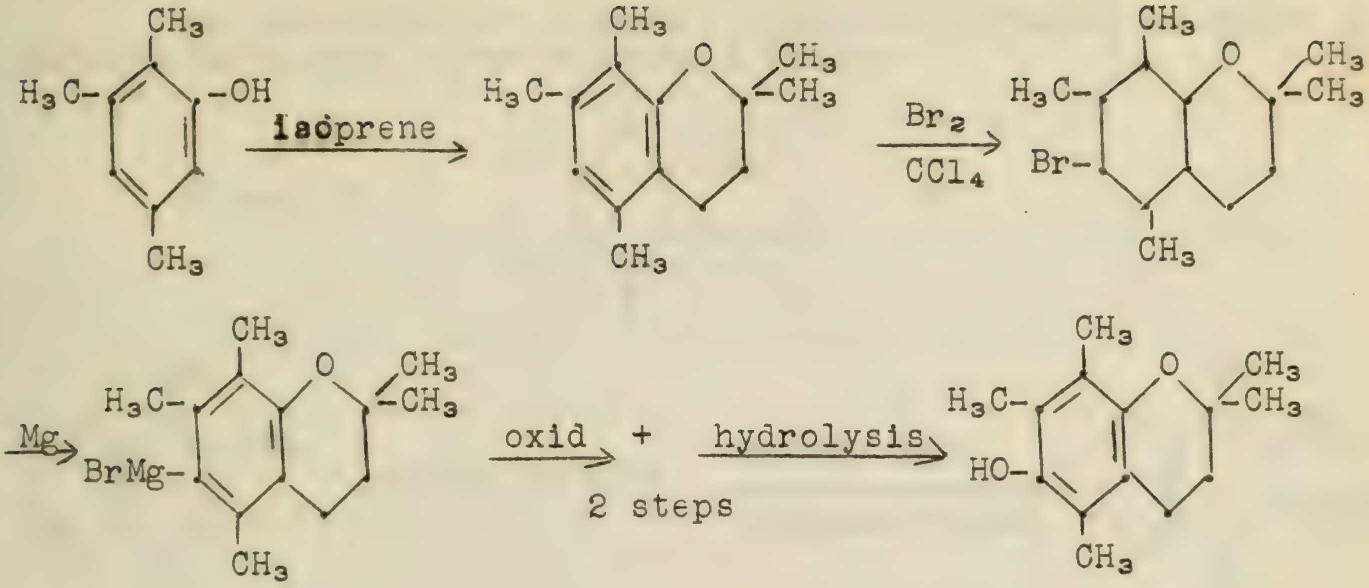
Consequently, syntheses were attempted employing phenols rather than hydroquinones, wherein the heterocyclic ring was built onto the phenol and the p-hydroxy group then introduced as the final step in the synthesis. For the introduction of the hydroxy group into position six (chroman nomenclature) three methods were investigated. In the first two of these the aim was the introduction of an amino group, either by nitration or by coupling with a diazonium compound, followed by reduction. It was then planned to convert the amino chroman to the hydroxy chroman by mild oxidation to the quinone, followed by reduction + recyclization.

V



The chroman V could be nitrated in good yield in the vacant ring position but the nitro chroman was very inert and could not be reduced by any method. The chroman V could not be coupled even when the most active coupling agents were used. Consequently, these two routes were abandoned.

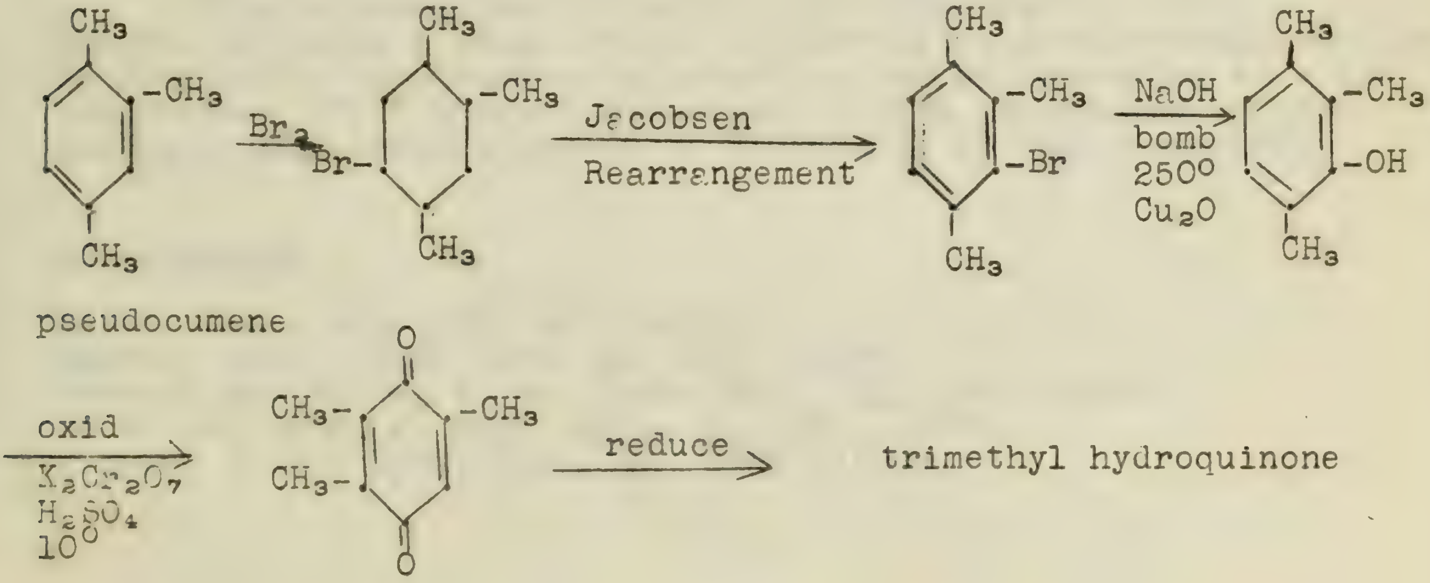
Greater success was had by synthesis via the bromo compounds - but the overall yields were very small.



While such syntheses appear to be promising as general methods of preparing p-hydroxy chromans, no tocopherols have as yet been synthesized by any of these methods. Likewise unsuccessful as yet are experiments leading to the synthesis of tocopherols without the use of phytol.

Synthesis of Alkylated Quinones

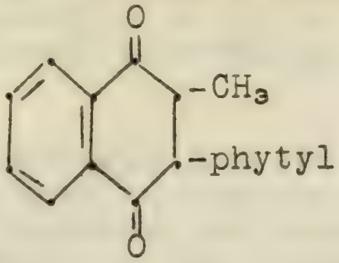
The synthesis of relatively large amounts of alkylated quinones and hydroquinones was at first a formidable task, but now these preparations can be said to be solved.



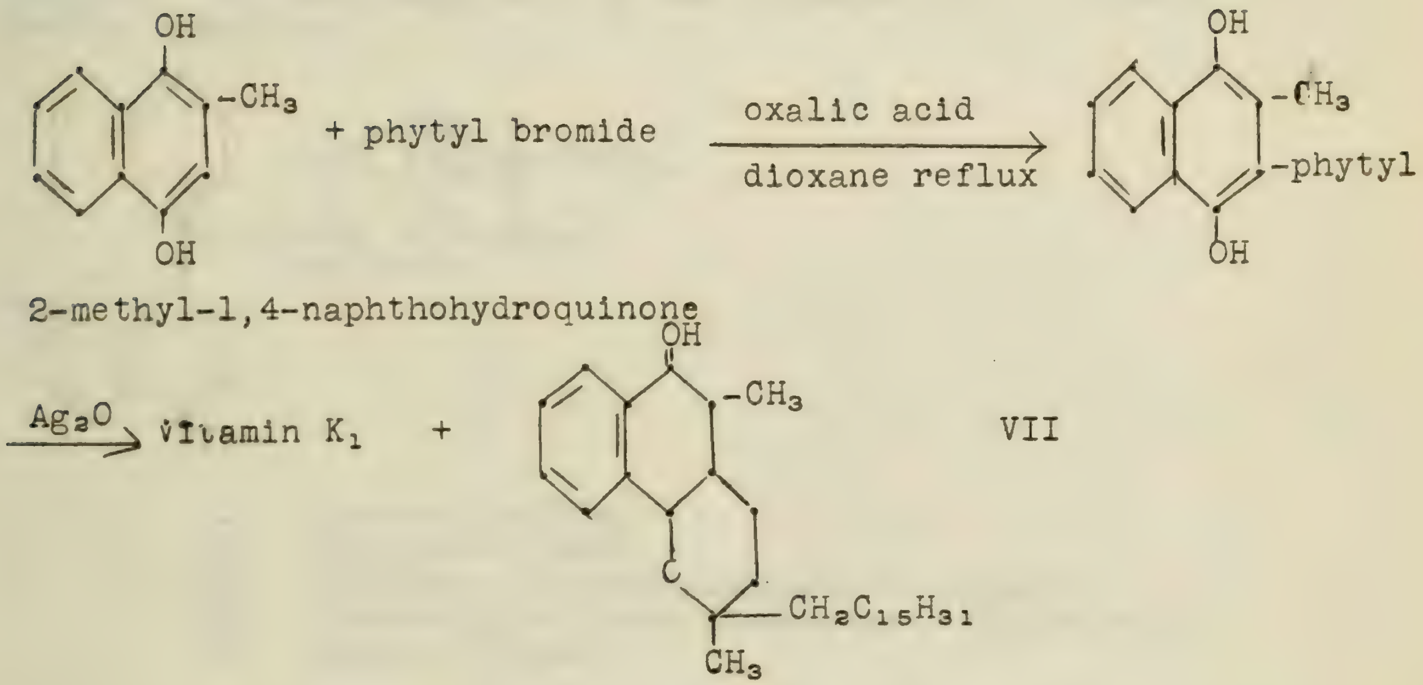
Vitamin K_1

The synthesis of vitamin K_1 has been effected by means of methods developed in the vitamin E field.

Vitamin K_1



VI



2-methyl-1,4-naphthohydroquinone

VII

Ring closure took place to form by-products (VII). Fieser, by using a large excess of 2-methyl-1,4-naphthohydroquinone to accelerate the bimolecular reaction and by operating at a low temperature (75°) where cyclization is slow, succeeded in producing a considerable amount of Vitamin K_1 by this reaction.

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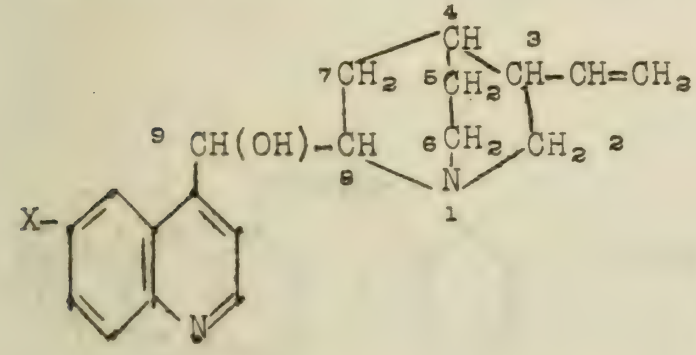
Reported by Henry Yuska
December 18, 1940

ANTI-MALARIALS

Recent successes in the field of anti-malarials have stimulated research, and there have been numerous publications. This is an attempt to describe a few of the most useful chemical agents and some of the most interesting synthetic work that was encountered.

Chemotherapy probably had its beginning in 1630 when cinchona bark was first used to prepare an anti-malarial. It was not until 1820 that quinine and cinchonine were isolated. They are the most important of the cinchona group of about twenty alkaloids.



I. Quinine ($X=OCH_3$)
II. Cinchonine ($X=H$)
III. Quinidine (stereoisomeride of quinine)
IV. Cinchonidine (stereoisomeride of cinchonine)
V. Cupreine ($X=OH$)

The dihydro derivatives (saturated side-chain at *3*) are found in traces. Quinine is the most useful member of this series as an anti-malarial.[1]

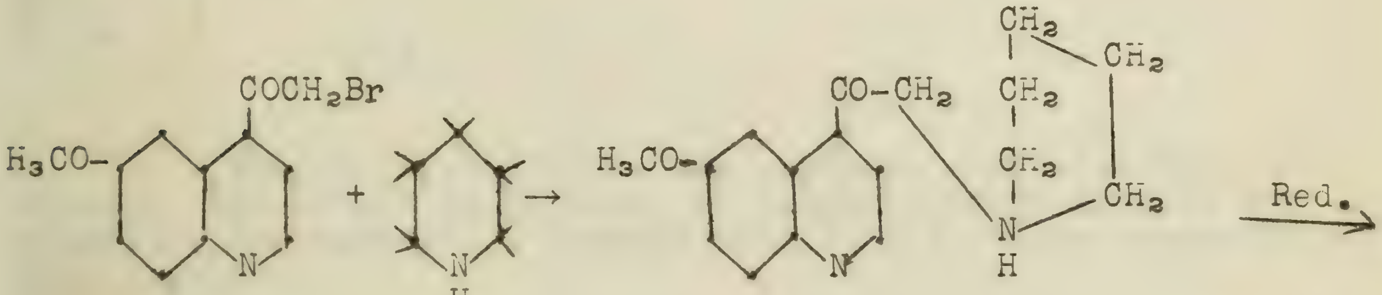
There are two functional phases of the malarial parasite, the *schizonts* (which cause the fever), and the sexual forms or gametocytes (which spread the disease). It has been found that a different drug is necessary to destroy each type. Thus, quinine is a *schizonticidal* drug and is useless for preventing the spread of malaria. After publication of the quinine formula by Rabe in 1908, both synthetic and degradative experiments were begun in an effort to find a more effective compound.

The therapeutic index (T/C) expresses the efficiency of any drug. *T* is the maximum tolerated dose (limited by toxicity) and *C* is the minimum curative dose. The tests are made according to a standard procedure, using canaries and Java sparrows infected with bird malaria.

The degradative experiments were of little value. Interconversion of several isomers produced compounds either no more active or not active at all. Conversion of the 7CHOH group to CHCl, CH_2, CO, or -CH=, led to inactivity. Demethylation lowered the degree of activity.

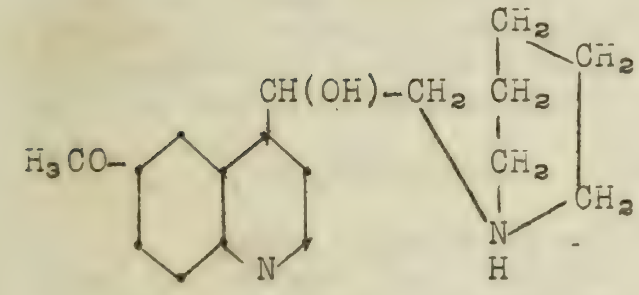
Synthesis of compounds similar to quinine was next attempted.

Kaufmann (1913, 1918) and Rabe (1917) prepared a series of compounds in which the right-hand (quinuclidine) ring was simplified. 4-Cyano quinoline (or the corresponding 6-methoxy compound) was condensed with CH_3MgI to give the 4-quinolylmethyl ketone. This was brominated to give the α-brom derivative which was condensed with an amine and then reduced to the carbinol.



VI

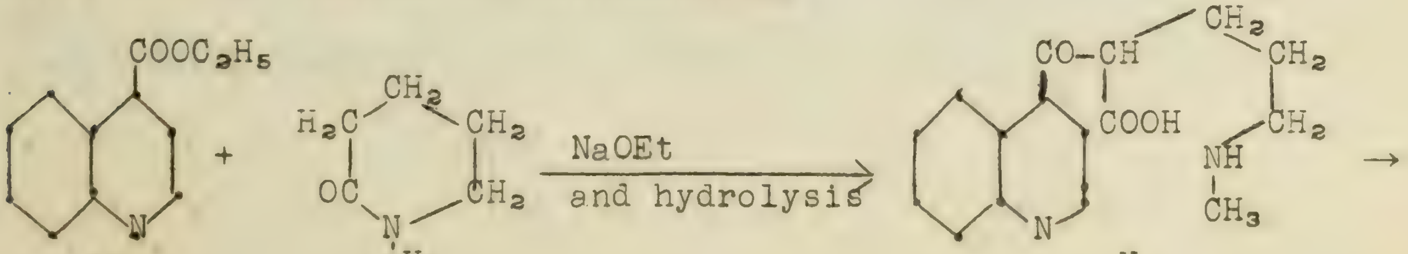
VII



VIII

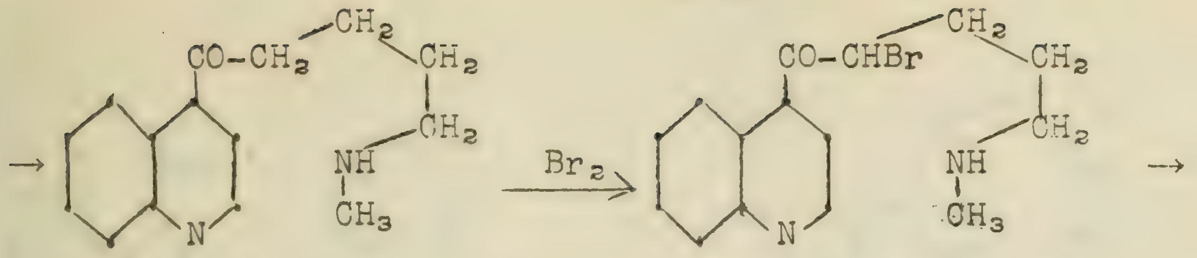
In spite of their close resemblance to quinine, these compounds were entirely inactive on malaria.

Another route has been followed using quininic acid ester and the lactams of amino-acids.



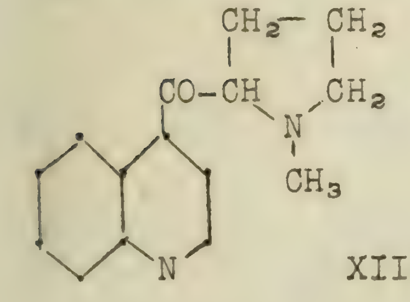
IX

X



XI

XII



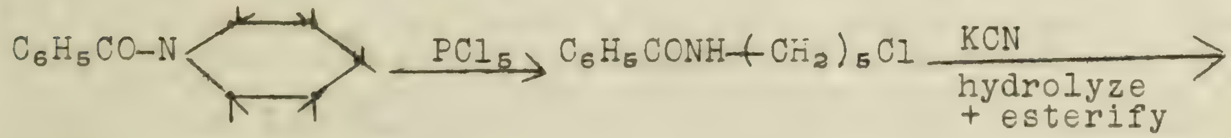
XIII

Reduction of XIII to the carbinol completes the synthesis. The method is general, so ε-amino acids produce α-piperidyl derivatives. (Compare with VIII.) These compounds were also inactive.

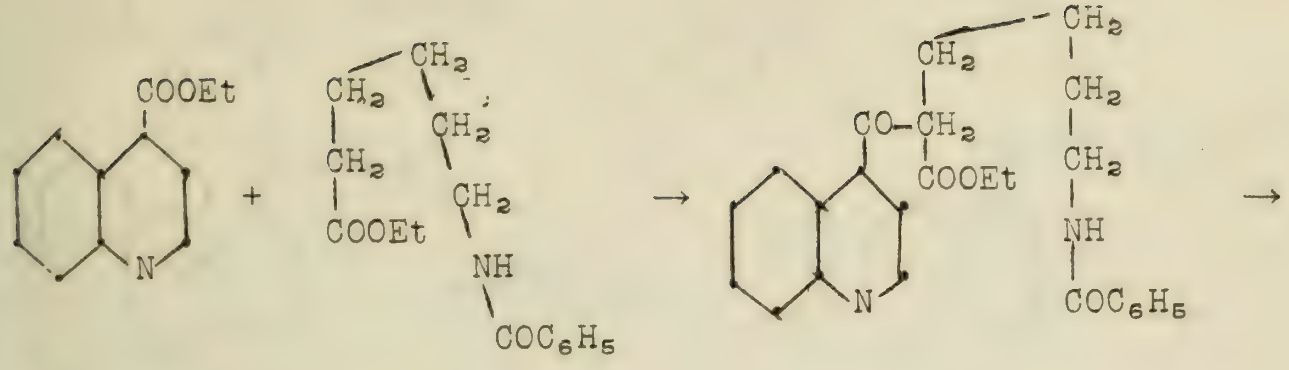
The γ-piperidyl compound was derived from cinchonine by the "hydramine fission" of Rabe and Schneider. When a salt of cinchonine is heated, it is isomerized to cinchotoxine -XIV [4-quinolyl-ω-(4-piperidyl)-ethyl ketone]. It was also inactive, as was the carbinol obtained by reducing it. This isomerization is apparently general for an amino nitrogen attached to a carbon α to a carbinol (ephedrine). It may be represented thus:

$$(R-CHOH-\overset{|}{C}H-\overset{|}{N}- \rightarrow R-CO-\overset{|}{C}H_2 \quad NH-)$$

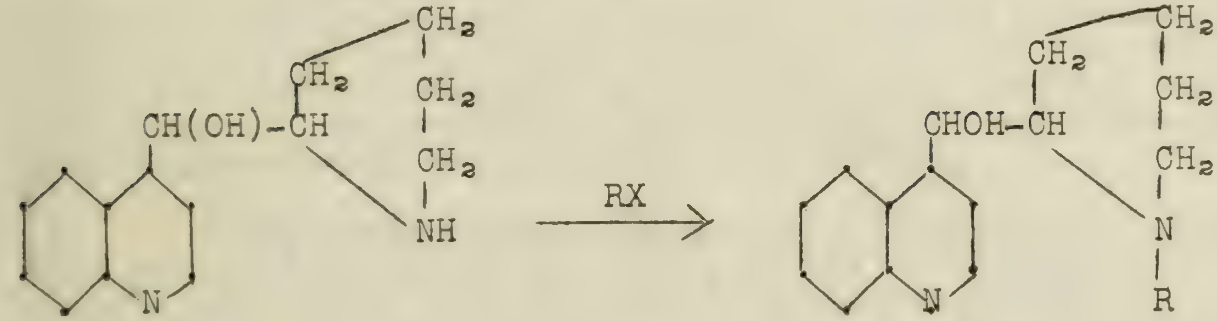
The inactivity of VIII, XIII, and XIV led Ainley and King to believe that the two rings should be more close together, so they prepared a series of 2-piperidyl-4-quinolyl carbinols.



$C_6H_5CONH(CH_2)_5-COOEt$



XV XVI XVII

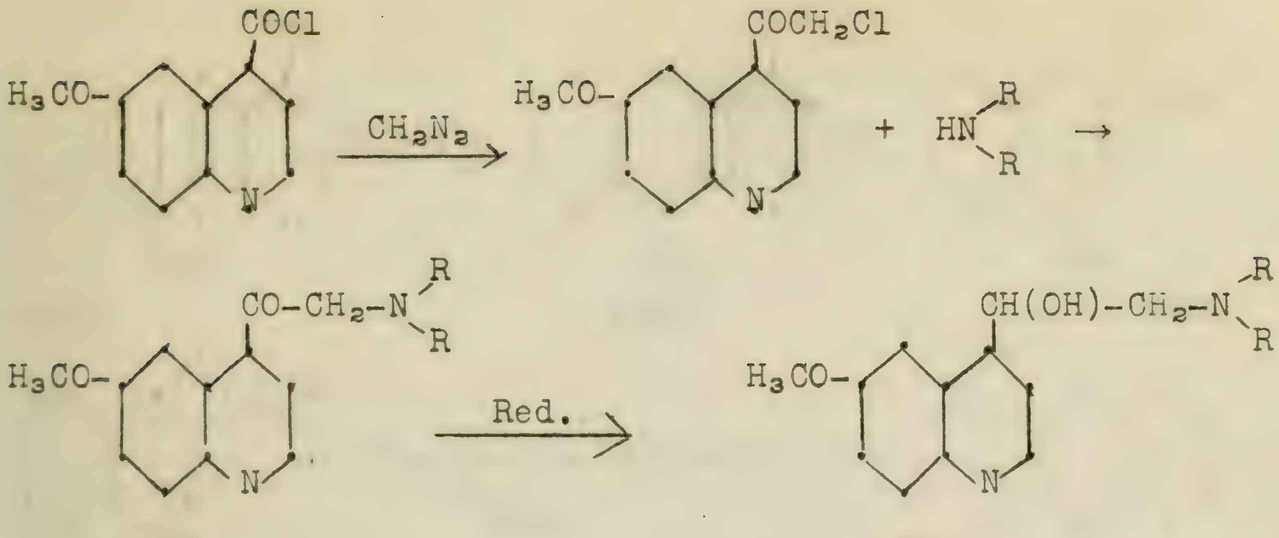


XVIII XIX

Compound XVII was converted into XVIII by hydrolysis, decarboxylation, bromination, and ring closure in the same way that XIII was prepared. The analogous 6-methoxy quinoline compound was also prepared.

The compounds XVIII were active anti-malarials, but the methyl, propyl, allyl, and butyl derivatives XIX were inactive.

Following up this work, King and Work prepared some similar 1,2-carbinol amines which were much more simple. The piperidine ring was replaced by a dialkylamino group which was still one carbon atom removed from the carbinol group. The dibutyl, diamyl, and dihexyl compounds (XXI) were active. Note that the dibutyl compound differs from dihydro quinine only by four H atoms. They are among the simplest substances to show anti-malarial activity. The synthesis starts with the 4-quinolyl-halomethyl ketone (VI) . Another method of preparing this intermediate is by reacting chinconinic acid chloride with diazomethane.



XX

XXI

The above series was repeated, substituting naphthalene for the quinoline ring. The naphthyl, methoxy naphthyl, and unsubstituted quinolyl derivatives were inactive, as were the lower and higher homologues of (XXI) (methyl, heptyl, etc.). This leads to the conclusion that the quinoline nucleus and the proper side-chains are essential for activivy.

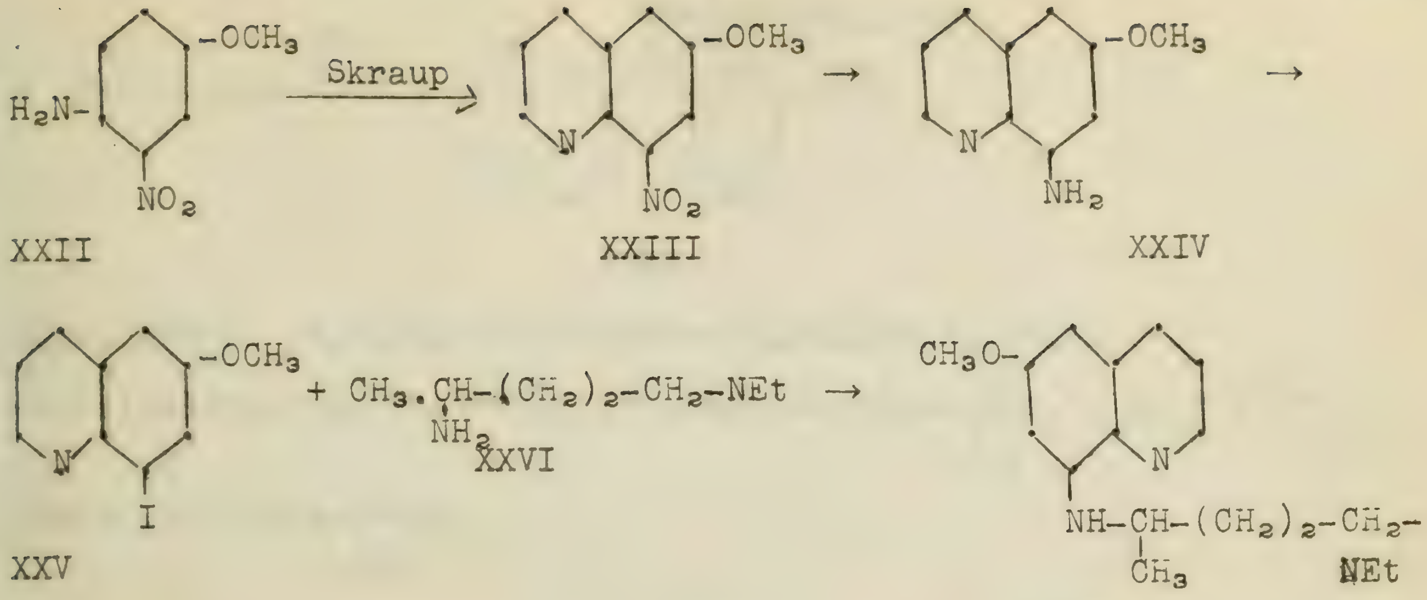
The lower dialkyl amines used in the above synthesis were prepared by either the $NaCN_2$ method or the p-nitroso dialkyl aniline reaction. A novel method was necessary for the dihexyl and diheptyl amines, however. Benzyl amine was alkylated with two moles of the alkyl bromide in good yield. The benzyl group was then reduced off quantitatively over PtO + glacial AcOH.

In another publication, Work has given support to the theory that the substituted quinoline nucleus is necessary. He prepared a series of compounds in which various other groups replaced the quinoline nucleus. (Aliphatic chain, biphenyl, dipiperidyl, tetrahydroquinolyl, and others.) All these compounds were inactive.

The total synthesis of dihydro quinine was reported by Rabe in 1931. (Gilman, page 1060) His compound proved to be identical with reduced quinine.

All the above work has been on compounds closely related to quinine. Notable successes have been achieved using quite different structures. Both methylene blue and solvarsan have some anti-malarial activity.

Schulemann, Schonhofer and Wingler noticed that the replacement of $-NMe_2$ on methylene blue by $-N(CH_3)(CH_2)_2NEt_2$ produced a compound of enhanced activity. Similar chains were then substituted in the 8-position of quinoline producing very active compounds. Thus (XXVII) plasmoquine, 8-(ω-diethyl aminoisoamyl)-amino-6-methoxy quinoline) was discovered. One of its syntheses (by Knunyantz) is as follows:

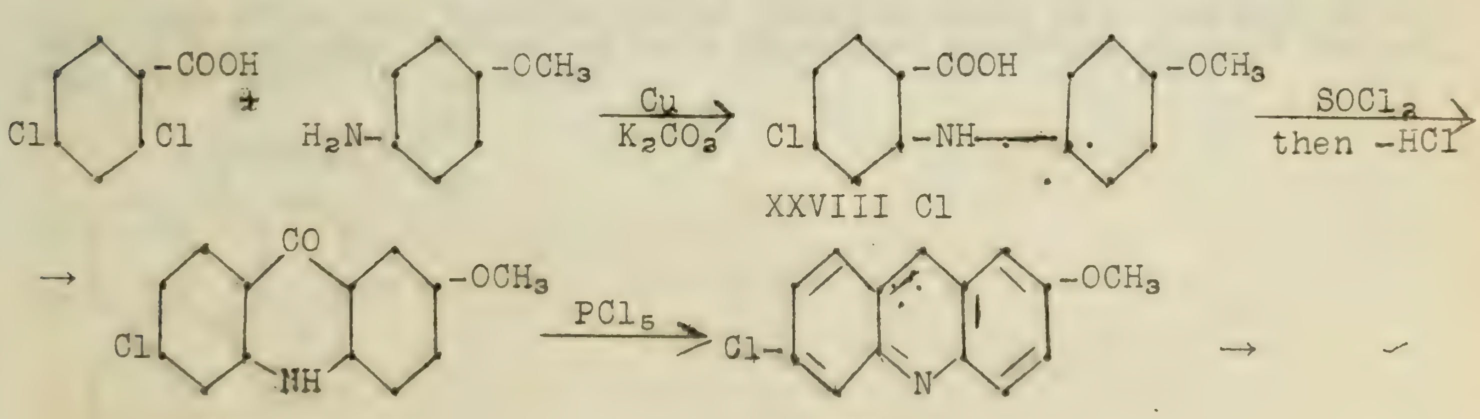


XXII XXIII XXIV

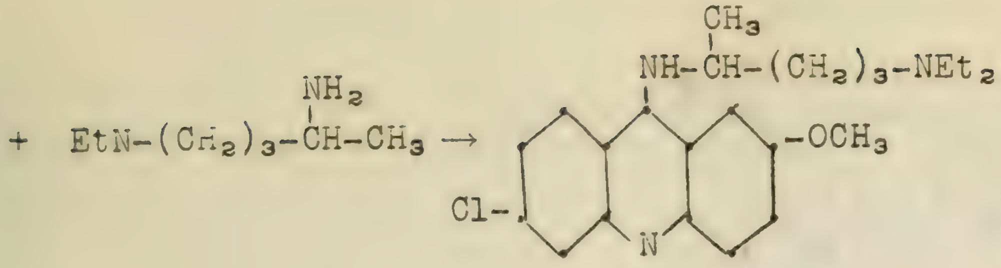
XXV XXVI XXVII

Plasmoquine has a chemotherapeutic index of 40, as compared with 4 to 10 for quinine. It is a gametocidal drug, and may therefore be used along with quinine to prevent the spread of malaria. It was selected as the most effective of a group of 6-alkoxy, 8-alkylamino quinolines, many of which exhibited activity.

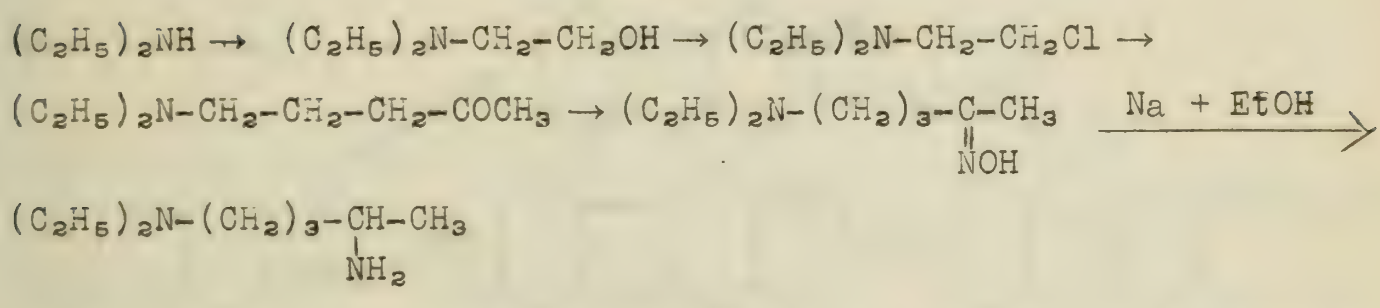
The first synthetic schizonticidal drug of any importance was reported by Mauss and Mietzsch. Working with acridine compounds containing the same dialkylamino-alkylamino side chain, they developed a potent drug now called "atebrin". [2-methoxy, 6-chloro, 9-4'-diethyl-aminoisoamyl)-amino acridine.] Cpd. XXXI. Here too this compound was the best of a group having varying chains on the ring. It has an index of 15 and may eventually replace quinine. The chlorine atom on position 6 is apparently essential for activity. A synthesis by Magidson and coworkers and by Knunyantz follows:



XXVIII XXIX XXX



XXXI



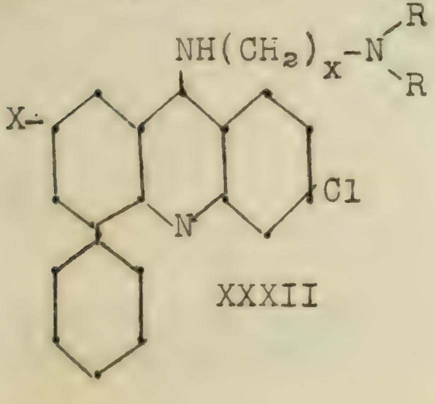
$$(C_2H_5)_2NH \rightarrow (C_2H_5)_2N{-}CH_2{-}CH_2OH \rightarrow (C_2H_5)_2N{-}CH_2{-}CH_2Cl \rightarrow$$

$$(C_2H_5)_2N{-}CH_2{-}CH_2{-}CH_2{-}COCH_3 \rightarrow (C_2H_5)_2N{-}(CH_2)_3{-}\underset{\underset{NOH}{\|}}{C}{-}CH_3 \xrightarrow{Na\ +\ EtOH}$$

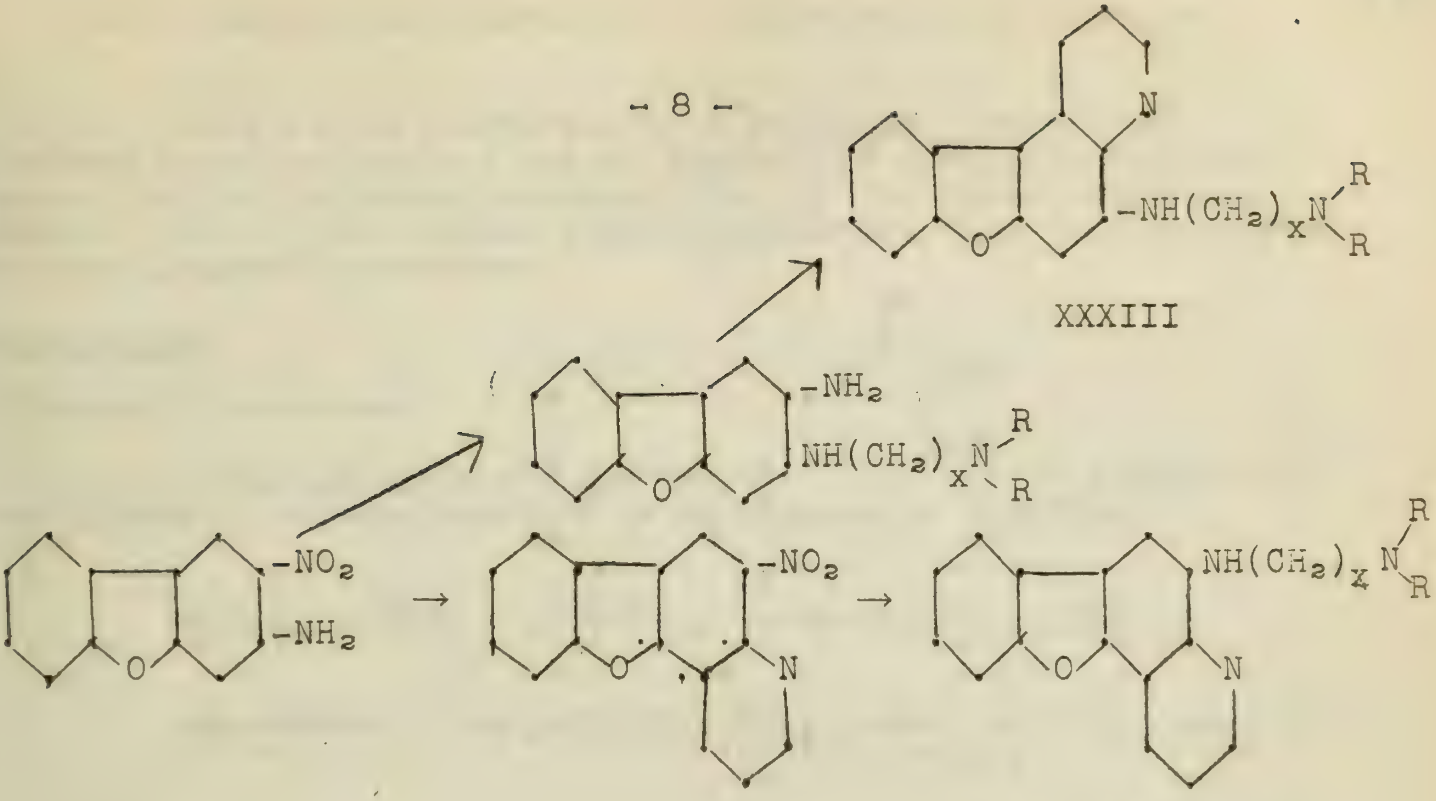
$$(C_2H_5)_2N{-}(CH_2)_3{-}\underset{\underset{NH_2}{|}}{CH}{-}CH_3$$

The diethylamino alkylamine used in the preparation of plasmoquine and atebrin is prepared in several ways, one of which is shown above. Hass and Huffman, who developed the nitroparaffins at Purdue, have recently reported a new synthesis which is claimed to be much cheaper than any previous one. 1,4-Dichloropentane (fractionated from a mixture of chlorinated pentanes) is reacted with 1 mole of NaI to give 1-iodo,4-chloropentane. With diethyl amine, this produces 1-diethylamino,4-chloro pentane. This compound is then treated with ammonia, or the procedure can be reversed and this halide condensed with a heterocyclic amine.

Dr. Adams has been working here with two types of compounds in this field. One type (XXXII) is closely related to atebrin. The properly substituted 2-amino biphenyl is condensed with dichlorobenzoic acid, as in (XXVIII), to produce this type, although difficulty has been encountered in effecting this condensation with substituted biphenyls. The other type is the dialkylamino alkylamino benzofuroquinoline (XXXIII and XXXIV). 2-Nitro, 3-amino dibenzofuran (by nitration) can be treated with an alkyl amine and then the nitro group reduced and cyclized by a Skraup reaction. Reversing this procedure produces another isomer. The type XXXIV is inactive.



XXXII



XXXIII

XXXIV

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Reported by R. B. Wearn
January 8, 1941

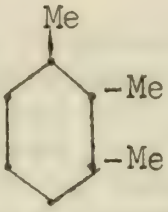
THE POLYALKYL BENZENES

L. I. Smith and coworkers ---- University of Minnesota

This research started in a reexamination of the Jacobsen reaction and has led to dependable synthetic methods for all of the polymethylbenzenes, two of the three triethylbenzenes, all of the higher polyethylbenzenes, and to a number of the ethylpolymethylbenzenes.

Preparations

Trimethyl benzenes:



Hemimellithene - 1,2,3-Me$_3$-Ø- -- Prepared by the Tiffeneau rearrangement of benzylmagnesium chloride.

$$\text{ØCH}_2\text{Cl} \xrightarrow{\text{Mg}} \xrightarrow{(\text{CH}_2\text{O})} \text{o-Me-ØCH}_2\text{OH} \xrightarrow{\text{HCl}}$$

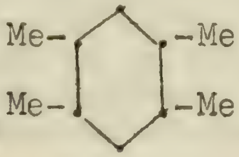
$$\xrightarrow[(\text{CH}_2\text{O})_n]{\text{Mg, then}} \text{1,2-Me}_2\text{-ØCH}_2\text{OH} \xrightarrow{\text{HCl}} \xrightarrow[\text{Cu(CrO}_2)_2]{\text{H}_2} \text{1,2,3-Me}_3\text{-Ø}$$

26% overall

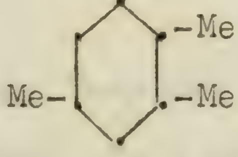
Pseudocumene (1,2,4-Me$_3$Ø) and Mesitylene -- Prepared by sulfonating the trimethylbenzene fraction obtained by methylating benzene or xylene with MeCl and AlCl$_3$; the fraction contains no hemimellithene. The mixed sulfonic acids are differentially hydrolyzed to the hydrocarbons, giving 10-12% of the fraction pure mesitylene and 35-37% pure pseudocumene.

Tetramethyl:

Durene (1,2,4,5-Me$_4$-Ø)

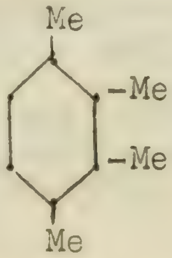


and Isodurene (1,2,3,5-Me$_4$-Ø)



Prepared from the tetramethylbenzene fraction from the xylene methylation, by freezing out most of the durene, then fractionally sulfonating and fractionally hydrolyzing twice. Yields are 20% and 45% respectively of the Me$_4$-Ø. Fraction.

Prehnitene: (1,2,3,4-Me$_4$-Ø)



Prepared by Jacobsen rearrangement of pentamethyl benzene in 65% yield.

Pentamethylbenzene and Hexamethylbenzene are obtained from the appropriate fraction from the methylation of xylene. Hexamethylbenzene is also obtained in 70% yield from the Jacobsen rearrangement of pentamethylbenzene.

The Jabobsen Reaction

This name has been given to the rearrangement of the polyalkylbenzenes, the halogenated polyalkylbenzenes, and the polyhalogenated benzenes which occurs when these substances are sulfonated and their sulfonic acids are allowed to stand in contact with sulfuric acid. The reaction consists in the migration of an alkyl group and/or a halogen atom, and was discovered by Oscar Jacobsen in 1886. Rearrangements caused by $AlCl_3$ do not constitute a phase of the Jacobsen reaction, but they are of interest because of the opposite orienting effects of the two reagents; $AlCl_3$ gives products in which the vicinal orientation of substituents is avoided, while sulfuric acid tends to produce the vicinal arrangement. The Jacobsen reaction does not appear to be an extensive reaction. With few exceptions it is limited to the halogen derivatives of benzene, the halogen derivatives of methylated benzenes, the tetramethylbenzenes, (durene and isodurene), pentamethylbenzene, the corresponding polyethylbenzenes, and to mixed alkyl benzenes. In general four substituents must be attached to the ring except when halogen alone is present. The substituents which have so far been shown capable of migration are I, Br, Cl, CH_3, C_2H_5, and SO_3H. No Jacobsen rearrangements are known in which an amino, nitro, acetyl, methoxyl, or carboxyl group is present in the molecule. Moreover, the conditions which bring about the rearrangements appear to be quite limited. Many reagents have been tried, but only some form of sulfuric acid has been found to be of general applicability, and it is not possible to replace more than a small proportion of the sulfuric acid by something else. The ease of rearrangement of various substituents change with the nature of the compounds.

Trimethylbenzenes: They are all stable to sulfuric acid.

Pentamethylbenzene: This undergoes the simplest type of Jacobsen reaction. The hydrocarbon first sulfonates and the sulfonic acid rearranges; this holds for all of the Jacobsen rearrangements. The reaction is intermolecular, involving a transfer of one Me group.

2 Me_5-Ø → Me_6-Ø + Prehnitene 5-sulfonic acid
74% 68%

+ 30% amorphous tarry material which is characteristic of all Jacobsen rearrangements except those of the Et_4-Ø's. It appears that the tar is the result of the action of H_2SO_4 on all organic materials present.

Tetramethylbenzenes:

Durene: $\xrightarrow[\text{intramolecular}]{\text{main}}$ prehnitene sulfonic + 15-30% tar

$\xrightarrow[\text{intermolecular}]{\text{V.small amount}}$ (Me_5-Ø-SO_3H) → Me_6-Ø + Prehnitene sulfonic
+
Pseudocumene 5-sulfonic acid

Isodurene: $\xrightarrow[\text{intra Me}]{\text{main}}$ prehnitene sulfonic + 30% tar
50%

$\xrightarrow[\text{amount inter.}]{\text{small}}$ (Me_5-ØSO_3H) → Me_6-Ø + Prehnitene sulfonic
+
Pseudocumene 5-sulfonic acid

Prehnitene: Stable to sulfuric

Hexamethylbenzene: Stable to sulfuric

Ethylbenzenes:

Tri: The mesitylene and pseudocumene analogues are stable to sulfuric acid and the vicinal compound is also presumably stable, though it is too difficult to synthesize to test it.

Tetra: The 1,2,4,5- and 1,2,3,5- isomers parallel in their behavior that of durene and isodurene respectively, the product from both being vic-Et_4-Ø-SO_3H. But in contrast to the methyl hydrocarbons, the rearrangement of the ethyl analogues was remarkably rapid and smooth; vic-Et_4-Ø-SO_3H resulted in 90-92% yields. Moreover, the usual tar was entirely absent, and little or no SO_2 was evolved. The 1,2,3,4- isomer is of course stable to sulfuric acid.

Penta: Here again the course of the rearrangement parallels that of the methyl analogue to give Et_6-Ø and vic-Et_4-Ø-SO_3H, and here also there is marked contrast in the speed and yield, the Et_5-Ø hydrocarbon giving only 10% Et_6-Ø and 15% vic-Et_4-Ø-SO_3H + large amounts of tar.

Hexa: Stable to sulfuric.

Ethyltrimethylbenzenes:

3-Ethylpseudocumene: Stable to sulfuric

5-Ethylpseudocumene and Ethylmesitylene: Rearrange into 3-ethylpseudocumene as the main reaction (25-35%); however, prehnitene is obtained (10%), 4- and 2-ethyl-*m*-xylene respectively (12%), pseudocumene and mesitylene respectively (5%).

Halogen Polymethyl Benzenes:

Halotrimethyl:

Chloromesitylene and 4-chlorohemimellithene are stable; 5-chlorohemimellithene was not available for study.

5- and 6-chloropseudocumene both rearranged to 3-chloropseudocumene the vicinal arrangement, in 70% and 45% yields respectively. Here an intramolecular shift of a Cl atom was involved since no polychloro products resulted.

5-Bromopseudocumene rearranged to 3-bromopseudocumene in 90% yield; but a small amount of tribromopseudocumene was obtained, indicating some intermolecular rearrangement.

Bromomesitylene rearranged entirely intermolecularly giving mesitylene and polybromomesitylenes.

Thus the halogen always migrates in the monohaltrimethyl benzenes if any rearrangement takes place, and the evidence is that the relative ease of migration is in the order Br > Cl > Me.

Halotetramethyl:

All the monochloro and monobromotetramethyl benzenes rearrange, and the relative ease of migration is Br > Me > Cl.

The bromo-Me_4-Ø's rearrange intermolecularly giving dibromo derivatives and a tetramethylbenzene sulfonic acid; if the acid is either durene or isodurene sulfonic, it then rearranges to give prehnitene sulfonic acid.

All the chloro-Me_4-Ø's give chloro-Me_5-Ø and 3-chloropseudocumene.

Reactions of the Tetra, Penta, and Hexaalkyl Benzenes:

Bromination: A very smooth reaction for all the polymethyl and polymethylbenzenes. The dibromoderivatives of the tetrasubstituted benzenes are solids and are formed without rearrangement or elimination of groups; unfortunately, they are of little value for configurational studies, as their mixed melting points show very slight depressions. Only prehnitene has been studied as to side chain bromination; in thie case the bromine goes onto an interior methyl group.

Nitration: Mononitro compounds are difficult if not impossible to prepare directly, but for the most part are available indirectly through mercuration.

Dinitro compounds can be prepared from all polymethyl and polyethyl benzenes, penta and hexa substituted molecules included; moreover, they are very good derivatives, giving large mixed melting point depressions.

Durene, isodurene, and prehnitene and their polyethyl analogues give normal dinitro compounds, merely filling the vacant spaces in the ring.

However, dinitration of the penta and hexa substituted benzenes shows a profound and very interesting difference between the methyl and ethyl analogues. Penta and hexamethylbenzene both give dinitroprehnitene exclusively with the ortho arrangement of nitro groups. But penta and hexaethylbenzene give dinitrodurene exclusively with the para orientation of nitro groups.

Mercuration: All of the tri and tetramethylbenzenes, and pentamethyl benzene are mercurated by mercuric acetate in methanol. Chloro, bromo, and iodomercury compounds are prepared by metathesis. The most important reaction of these mercury compounds is that with nitrosyl chloride to give nitroso compounds in high yields; these nitroso compounds in turn give the amino compounds by reduction. Also the mononitro derivatives are usually obtainable by treating the corresponding acetoxymercury derivatives with nitric acid.

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J. Org. Chem., 2, 112 (1937).

Reported by Carl M. Smith
January 15, 1941

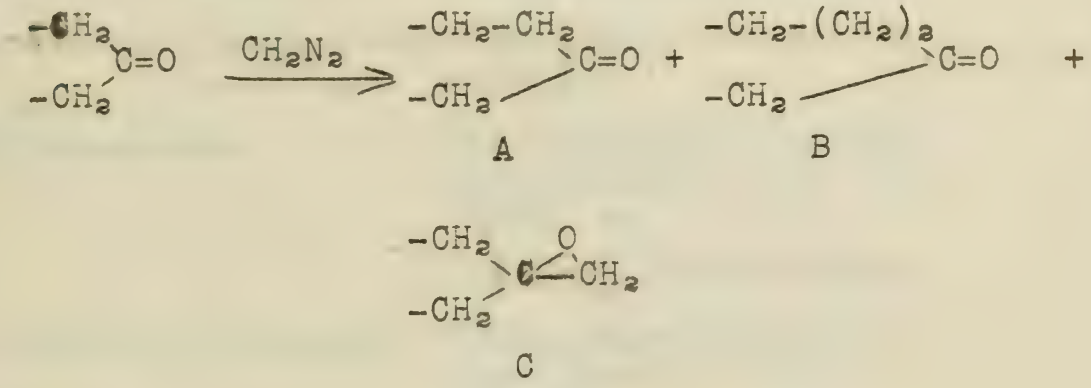
RING EXPANSION METHODS

Types Considered:

- I. Diazomethane Method
- II. Pinacol Rearrangement
- III. Demjanow Rearrangement
- IV. Indandione to Dihydroxynaphthalene Rearrangement
- V. Wagner Rearrangement
- VI. Pyrrole-Pyridine Expansion
- VII. Hydrocarbon Isomerization
- VIII. Miscellaneous

I. Diazomethane Method

A. Type reaction:



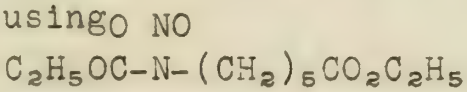
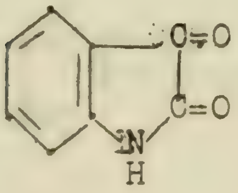
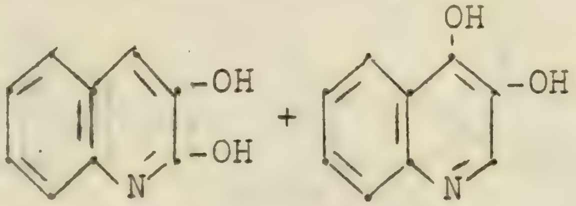
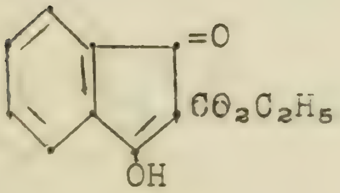
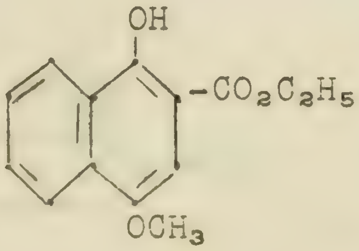
B. Procedure:

1. Laboratory: Add the ketone to an ethereal solution of diazomethane (containing a little alcohol as catalyst) until yellow color disappears.

2. Industrial: N-nitrosmethylurethan is added to a solution of the ketone in alcohol containing an alkaline catalyst, e.g. potassium carbonate.

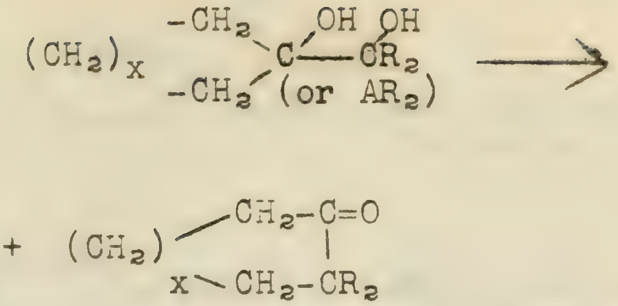
C. Examples:

	Starting Material	Products and Yields	Remarks	Reference
(1)	cyclopentanone	cycloheptanone or 43% "suberone"	(two mols CH_2N_2) Proc. 1	4
(2)	cyclohexanone	cyclopeptanone 52% +	cyclooctanone 8% + oxide 6% Proc. 1	4

(3)	cyclohexanone	cycloheptanone 63%		6
(4)	cycloheptanone	cyclooctanone 45%	Procedure 2	
(5)	cyclooctanone	cyclononanone 20%		
(6)	cyclononone	cyclodecanone 20%		
(7)	cyclohexanone	2-methylcycloheptanone	diazoethane	8
(8)	3-methylcyclohexanone	3-and 4-methyl-cycloheptanones		8
(9)	4-methylcyclohexanone	4-methylcycloheptanone		8
(10)	4-methoxycyclohexanone	4-methoxycycloheptanone 41%		7
(11)	cyclohexanone	2-(-carboethoxybutyl)-cycloheptanone 50% using  $C_2H_5O\overset{O}{C}-\overset{NO}{N}-(CH_2)_5CO_2C_2H_5$		7
(12)	2-chlorocyclohexanone	2-chlorocycloheptanone (nearly quantitative)		8
(13)	2-chlorocyclohexanone	2-chloro-7-methyl-cycloheptanone		8
(14)	2-cyclohexanone	only resin		9
(15)	fluorenone	9-methoxyphenanthrene 50% + di-(9-phenanthryl)-ether		
(16)	 isatin			31
(17)	 an oxindone carboxylic ester			31

II. Pinacol Rearrangement

A. Type reaction:

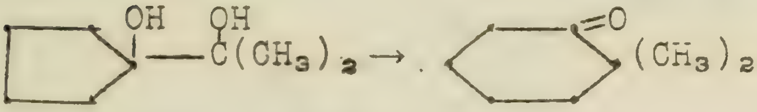


B. Procedure:

Meerwein uses cold, concentrated sulfuric acid, which, he states, gives minimum diene formation and has also the advantage of polymerizing the diene formed.

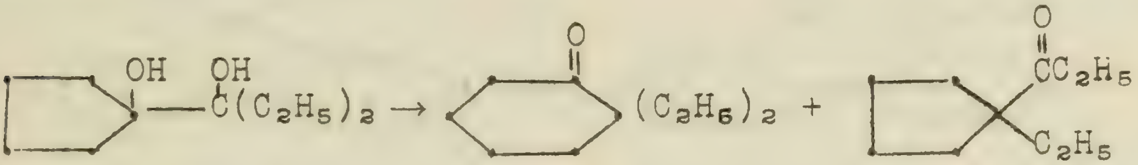
C. Examples:

(1)



55% sole product
Reference 15.

(2)



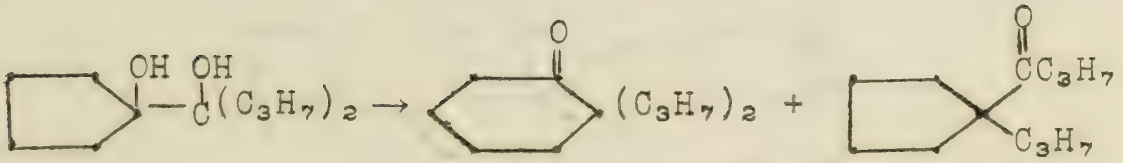
(prepared in 72%)

1 : 10 at 0° combined yield greater than 30%

4 : 7 at 20° 30% combined yield

Reference 13.

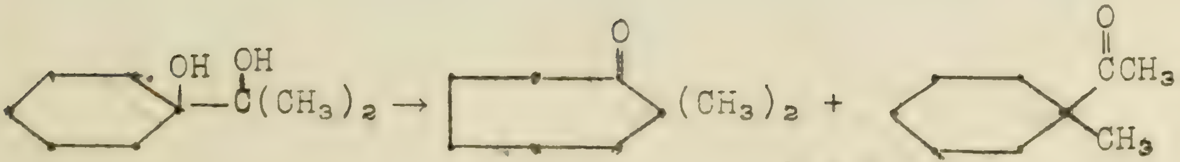
(3)



64:36

50% combined yield
Reference 13

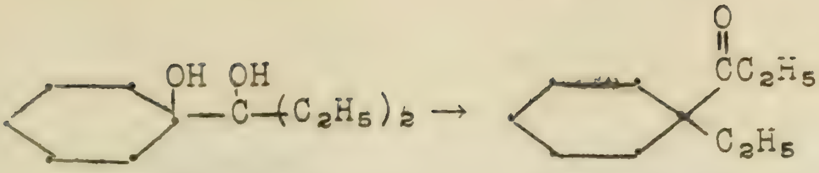
(4)



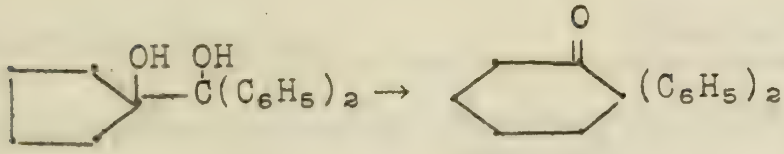
1 : 2

(prepared in 94%)

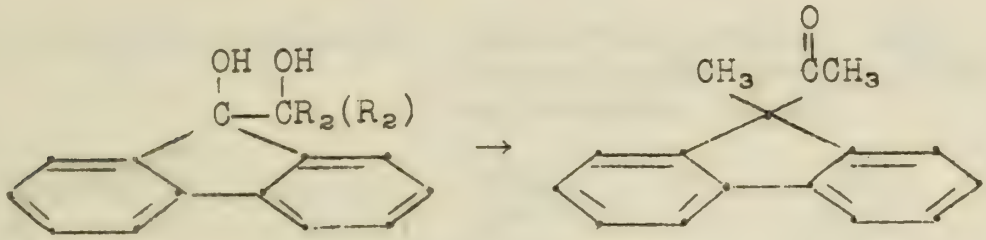
20% combined yield
Reference 13

(5) 

20% sole product
Reference 18

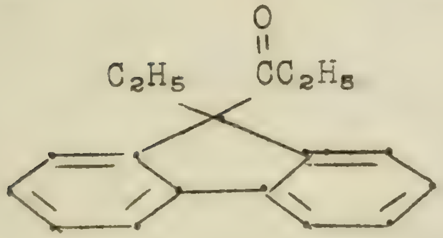
(6) 

almost quantitatively
Reference 12

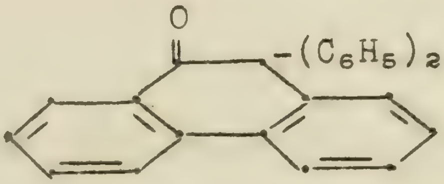
(7) 

or

sole product



but



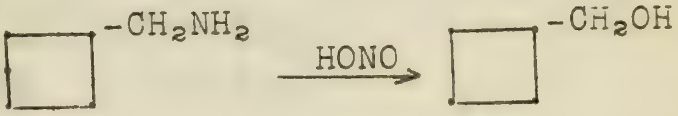
sole product

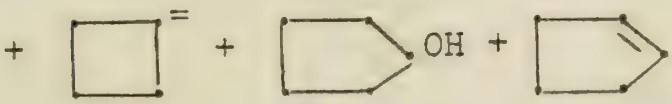
sole product

Reference 12

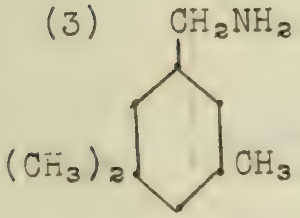
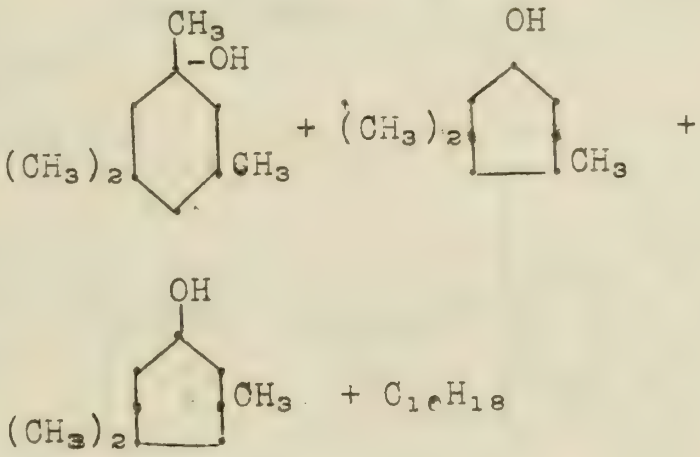
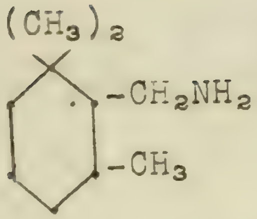
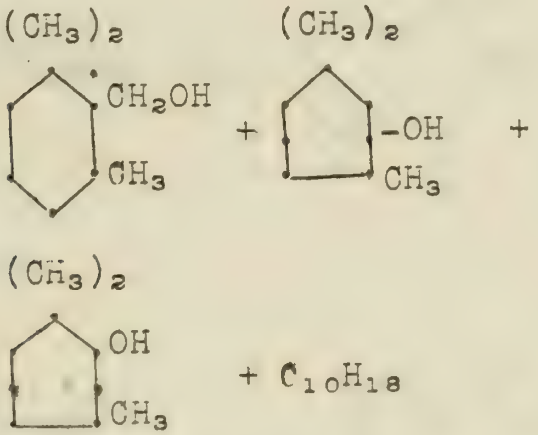
III. Demjanow Rearrangement

A. Type reaction: (1)



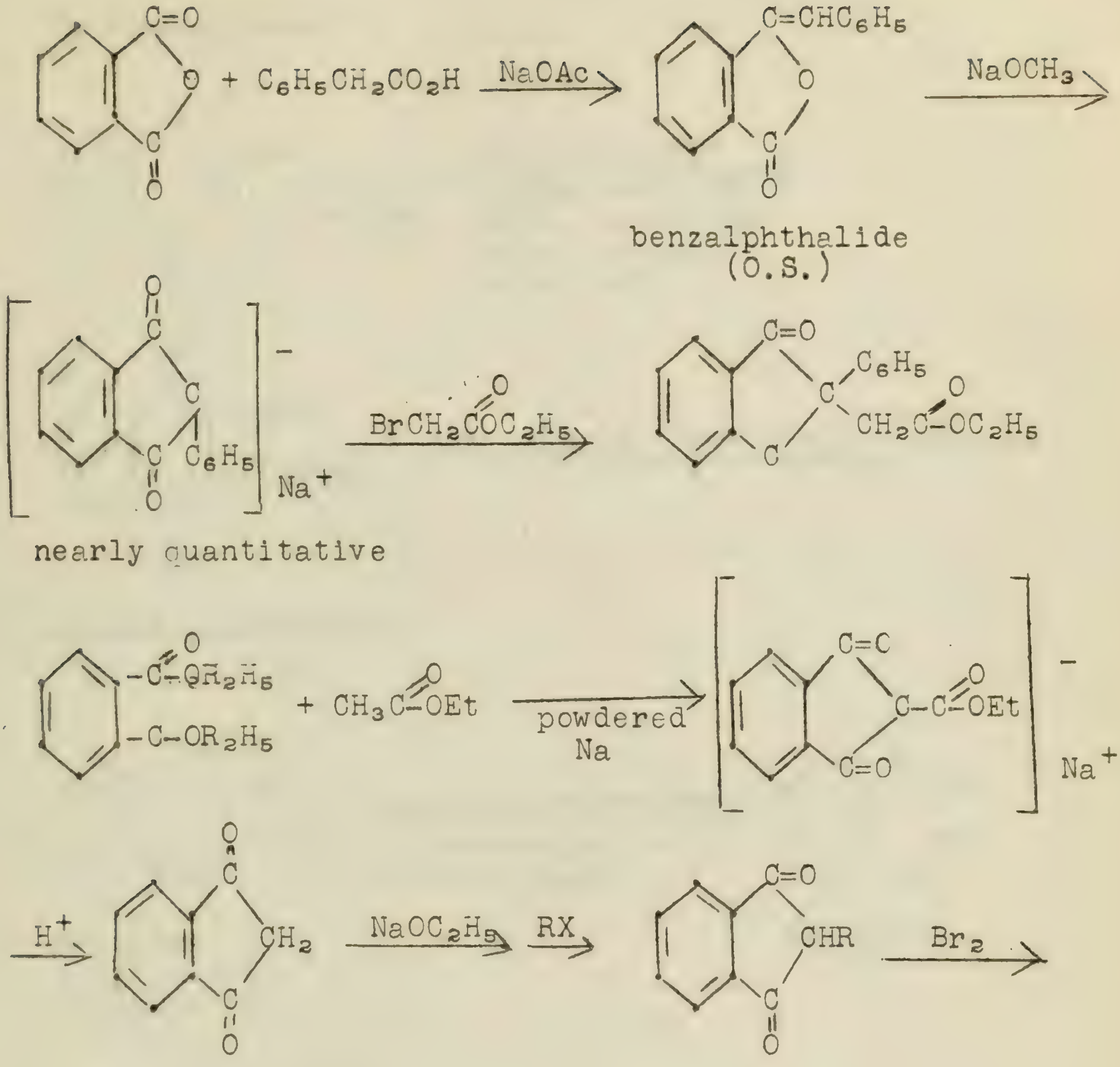


B. Examples:

Starting Material	Products	Reference
(1) cyclohexylmethylamine	cycloheptanol 58%, cycloheptene 21%	2
(2) cyclooctylmethylamine	cyclooctyl carbinol 26%, 1-methylcyclooctene-1 33%, cyclononanol 17.5%	2
(3) 		3
(4) 		3

IV. Indandione to Dihydroxynapthalene Rearrangement (25)

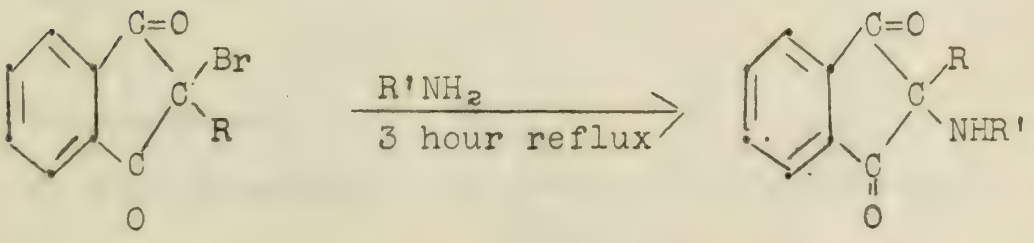
A. Synthesis of indandiones:



benzalphthalide
(O.S.)

nearly quantitative

diketohydrindene

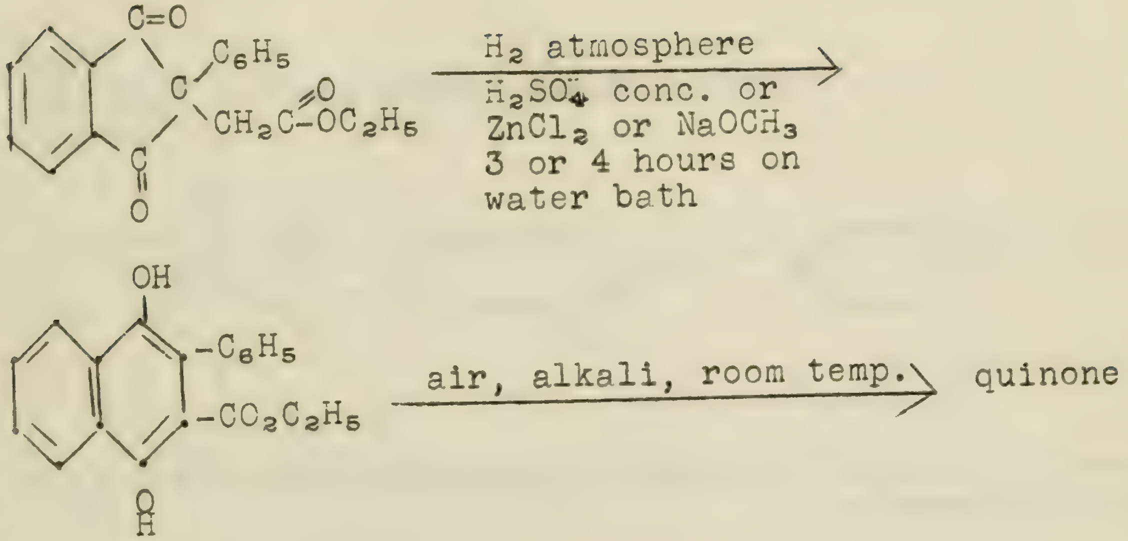


Yield on bracketed reactions

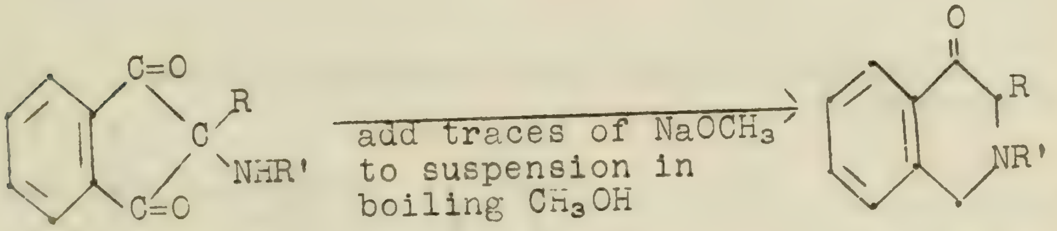
If: $R=R'C_6H_5$ 50%
If; $R=C_6H_5$, $R'=C_3H_7$ 30%

Alternative synthesis; rearrangement of alkylidine phthalide

B. Rearrangement:

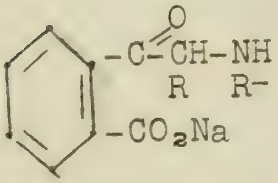


almost quantitative



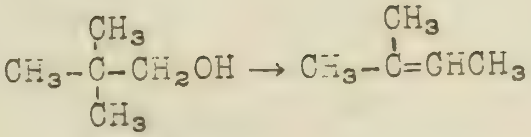
85% yield

resistant to
acid, alkali
ruptures to



V. Wagner Rearrangement

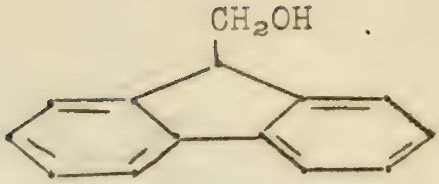
A. Type Reaction:



$$CH_3-\overset{CH_3}{\underset{CH_3}{C}}-CH_2OH \rightarrow CH_3-\overset{CH_3}{C}=CHCH_3$$

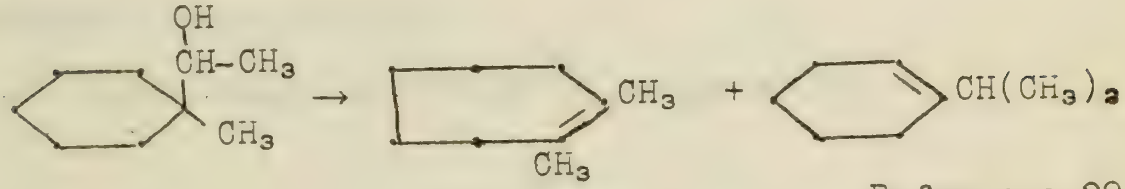
B. Examples:

(1) 9-formylfluorene $\xrightarrow[\text{aluminum isopropoxide}]{}$



$\xrightarrow[\text{boiling xylene}]{P_2O_5}$ phenanthrene quantitatively

(2)



Reference 29

(3) cyclopropyl and cyclobutyl carbinols → cyclobutyl and cyclopentyl bromide

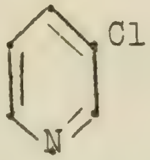
Reference 30

(4) Pinene → bornyl chloride

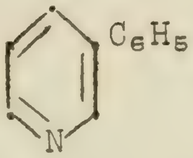
VI Pyrrole - Pyridine Expansion and Indole Expansions

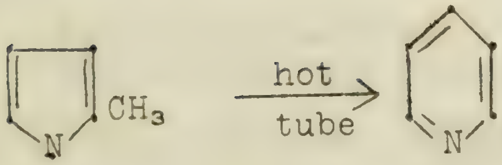
Reference 31

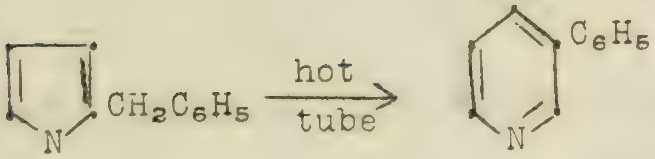
pyrrole $\xrightarrow[\text{NaOEt}]{CHCl_3}$

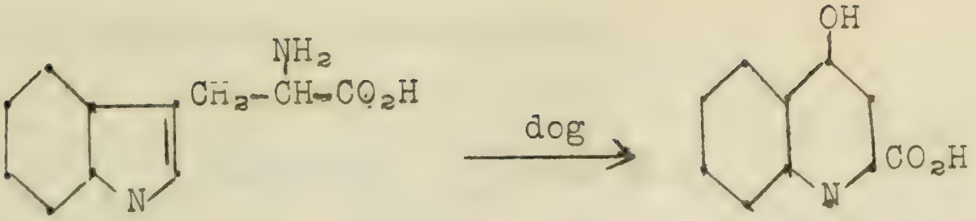


$\xrightarrow[\text{NaOEt}]{C_6H_5CHCl_2}$







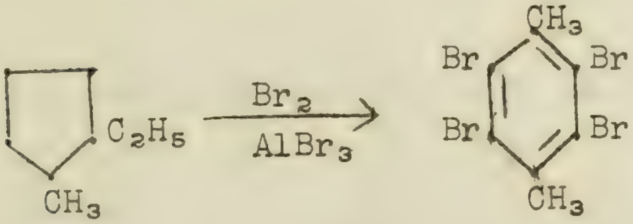


tryptophane   Kynwienic acid

VII. Hydrocarbon Isomerization

A. Ring Expansion During Dehydrogenation

(1)

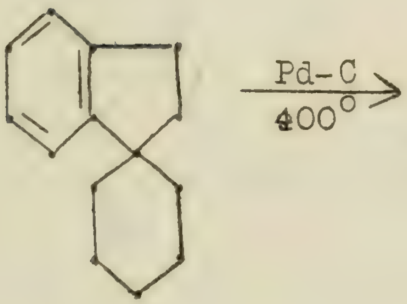


Reference 24

(2) various hydrindene derivatives $\xrightarrow[\text{above } 450^{\circ}]{\text{Pd-charcoal}}$ a little naphthalene

Reference 23

(3)



phenanthrene + anthracene

Reference 32

B. Ring Expansion without Dehydrogenation

Pines and Ipatieff carried out with yields of 80% or more the following rearrangements:

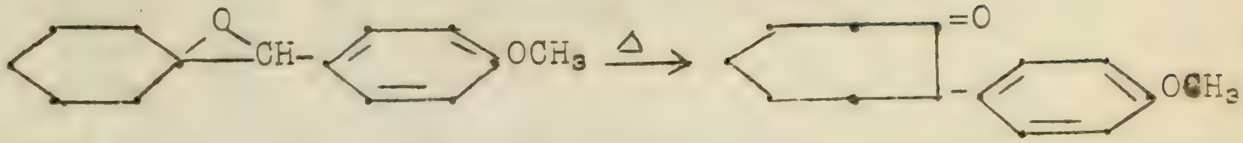
(1) ethylcyclopentane $\xrightarrow[\substack{50^{\circ} \\ 18 \text{ hrs.}}]{AlCl_3}$ methylcyclohexane

(2) n- and sec-propylcyclopentane → 1,3-dimethylcyclohexane

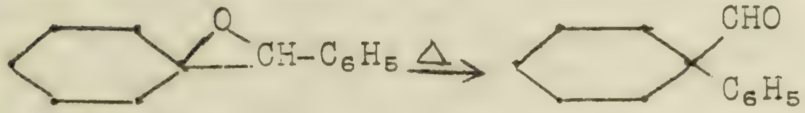
(3) n-, sec- and t-butylcyclopentane → sym-trimethylcyclohexane

VIII. Miscellaneous

A. Semibenzoin rearrangement

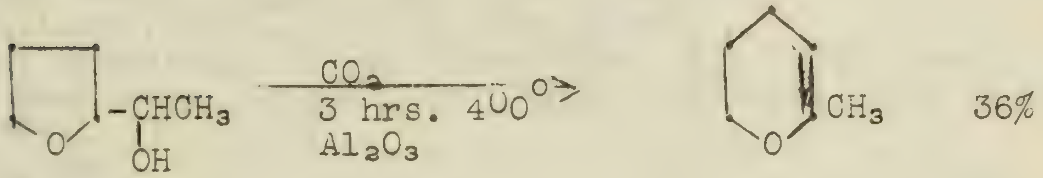


Reference 19



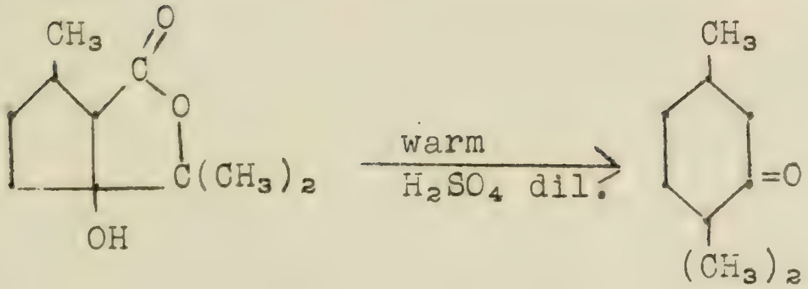
Reference 19

B. Methyltetrahydrofuryl carbinol dehydration



C.

Reference 17



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Reported by G. D. Jones
January 8, 1941

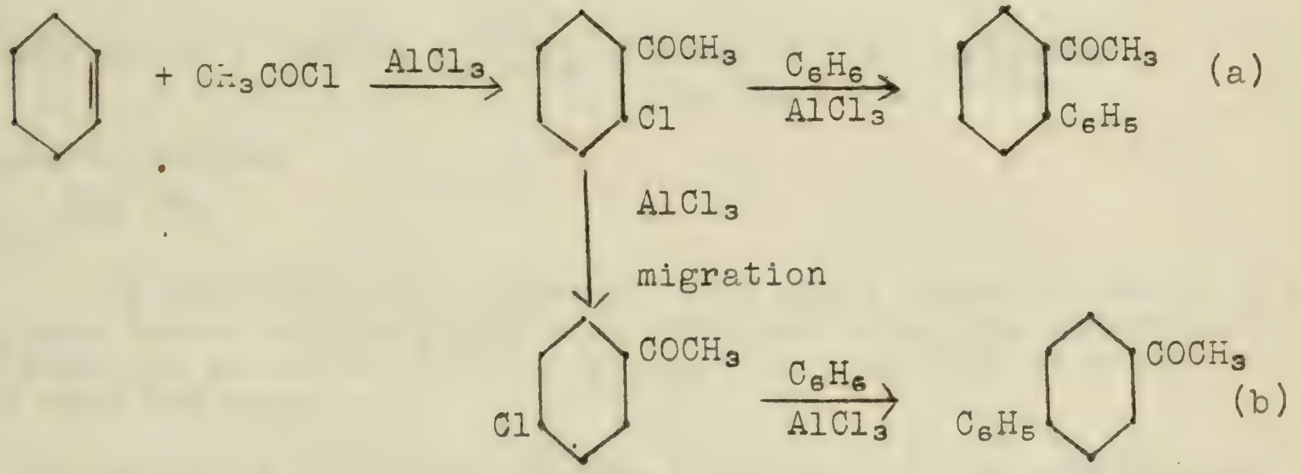
THE MIGRATION OF HALOGEN ATOMS IN CARBON CHAINS AND RINGS

Wieland and Bettag showed that β-chloroketones could be prepared by the condensation of acid chlorides and olefins in the presence of aluminum chloride.

I $$CH_2{=}CH_2 + ClCOCH_3 \xrightarrow{AlCl_3} ClCH_2CH_2COCH_3$$

In 1935 Nenitzescu and co-workers used this reaction with the idea of further reacting the chloroketone with benzene in the presence of aluminum chloride. An example of their experimental procedure was the addition of cyclohexene to acetyl chloride and aluminum chloride in carbon disulfide at -15°, removal of the carbon disulfide layer, and addition of benzene and more aluminum chloride, after which the mixture was heated at 40° for five hours. But examination of the product showed that the phenyl group, instead of entering into the 2-position, previously occupied by the chlorine atom (IIa), was in the 4-position to the acetyl group (IIb).

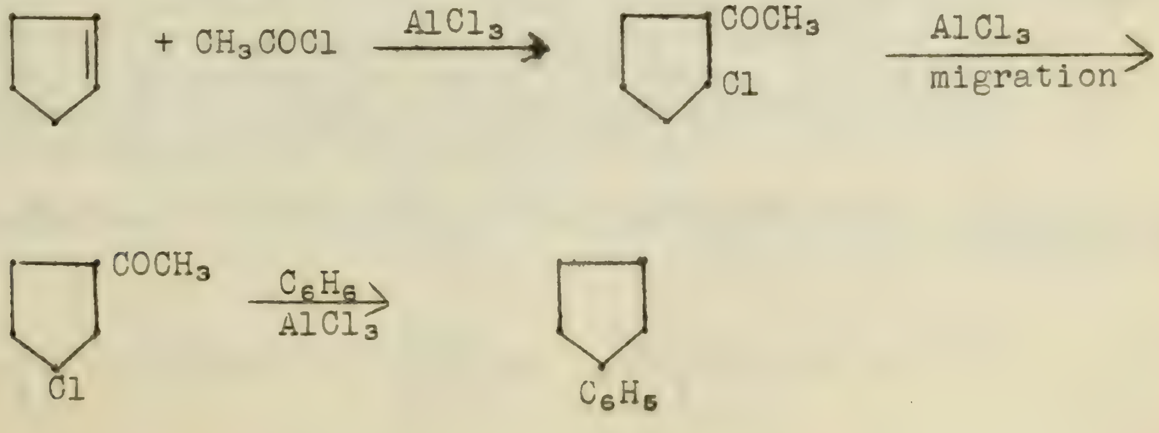
II



Under the influence of aluminum chloride the chlorine atom had migrated. The migration was quantitative; i.e., no other reaction product than the 4-phenyl compound could be isolated.

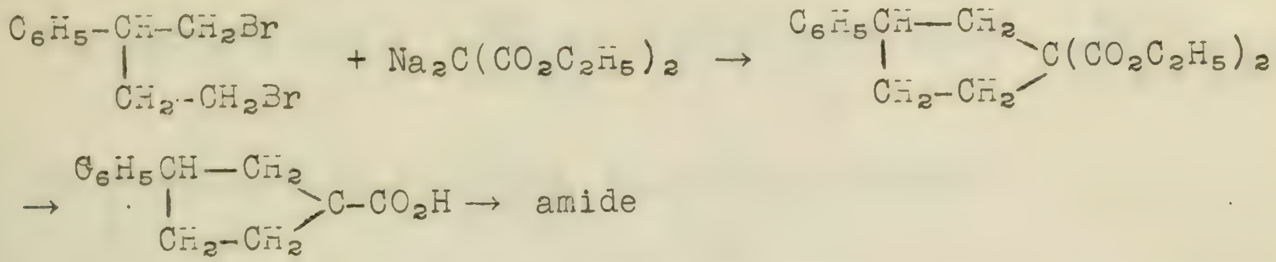
If the migration of halogen atoms in the cyclohexane ring was a general reaction, then a similar shift should take place to the 3-position in the cyclopentane series. Such proved to be the case:

III



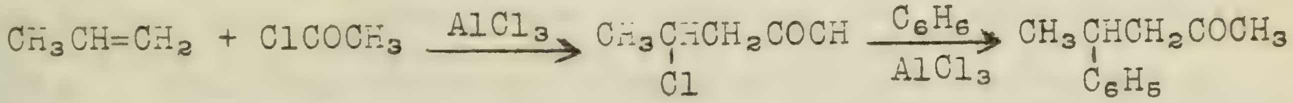
The 3-phenylacetylcyclopentane was oxidized to the carboxylic acid with hypobromite solution, and the amide was identical with that prepared by synthesis:

IV



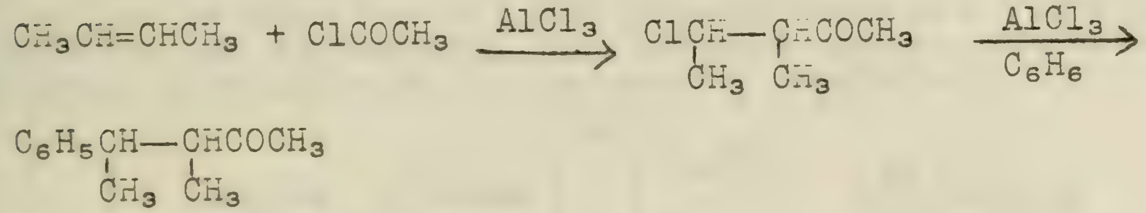
Transferring their interests from cycloparaffin structures to the aliphatic series, Nenitzescu and co-workers found that no migration occurred in the following reactions:

V



$$CH_3CH{=}CH_2 + ClCOCH_3 \xrightarrow{AlCl_3} CH_3\underset{Cl}{CH}CH_2COCH \xrightarrow[AlCl_3]{C_6H_6} CH_3\underset{C_6H_5}{CH}CH_2COCH_3$$

VI

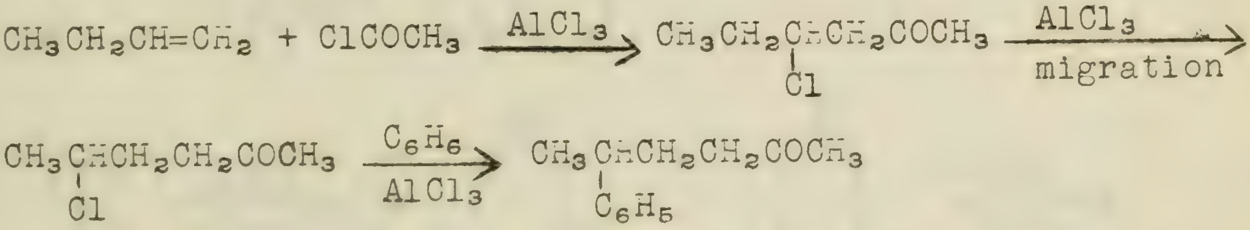


$$CH_3CH{=}CHCH_3 + ClCOCH_3 \xrightarrow{AlCl_3} \underset{CH_3}{ClCH}-\underset{CH_3}{CH}COCH_3 \xrightarrow[C_6H_6]{AlCl_3}$$

$$C_6H_5\underset{CH_3}{CH}-\underset{CH_3}{CH}COCH_3$$

It was suspected, however, that while migration would not take place from a -CHCl- group to a terminal $-CH_3$, the chlorine atom would shift to an adjacent $-CH_2-$ group. The reaction with butene-1 showed this was true.

VII

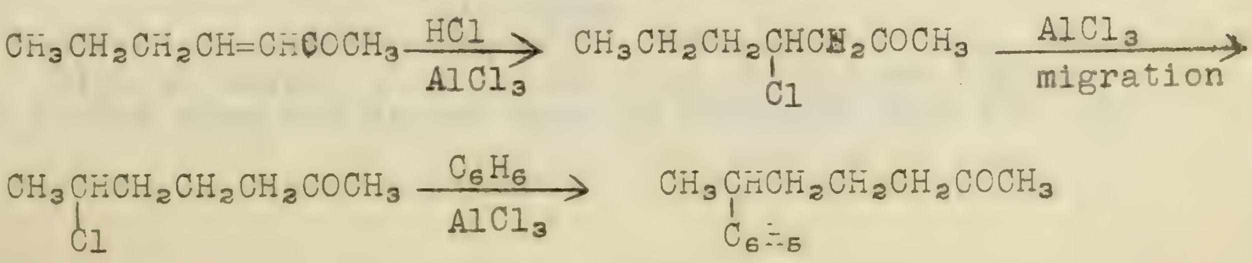


$$CH_3CH_2CH{=}CH_2 + ClCOCH_3 \xrightarrow{AlCl_3} CH_3CH_2\underset{Cl}{CH}CH_2COCH_3 \xrightarrow[migration]{AlCl_3}$$

$$CH_3\underset{Cl}{CH}CH_2CH_2COCH_3 \xrightarrow[AlCl_3]{C_6H_6} CH_3\underset{C_6H_5}{CH}CH_2CH_2COCH_3$$

It was quite difficult to work with longer chains in this fashion, and α,β-unsaturated ketones were substituted for the chloroketones. Here it was assumed that addition of hydrogen chloride first produced a β-chloroketone, which condensed with benzene in a true Friedel-Crafts reaction; the over-all reaction was not a simple addition of benzene to the double bond. By this procedure, definite migration was shown, as evidenced by the production of 6-phenyl-heptanone-2 from butylidene-acetone:

VIII

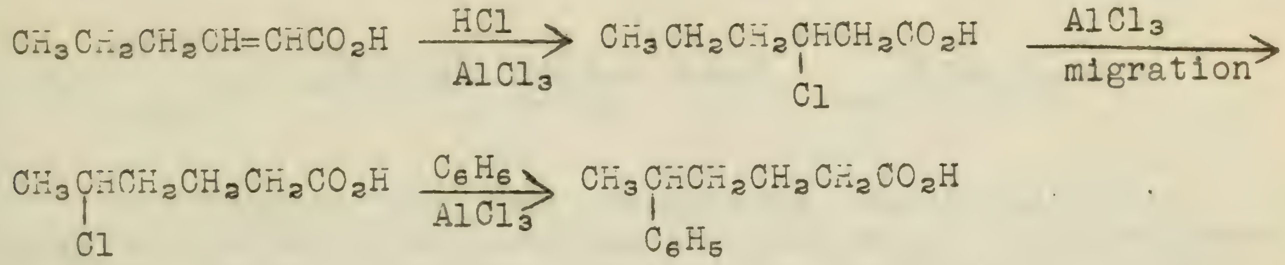


$$CH_3CH_2CH_2CH{=}CHCOCH_3 \xrightarrow[AlCl_3]{HCl} CH_3CH_2CH_2\underset{Cl}{CH}CH_2COCH_3 \xrightarrow[migration]{AlCl_3}$$

$$CH_3\underset{Cl}{CH}CH_2CH_2CH_2COCH_3 \xrightarrow[AlCl_3]{C_6H_6} CH_3\underset{C_6H_5}{CH}CH_2CH_2CH_2COCH_3$$

Use of α,β-unsaturated acids in place of the ketones gave similar results; α,β-hexenoic acid yielded δ-phenylcaproic acid:

IX

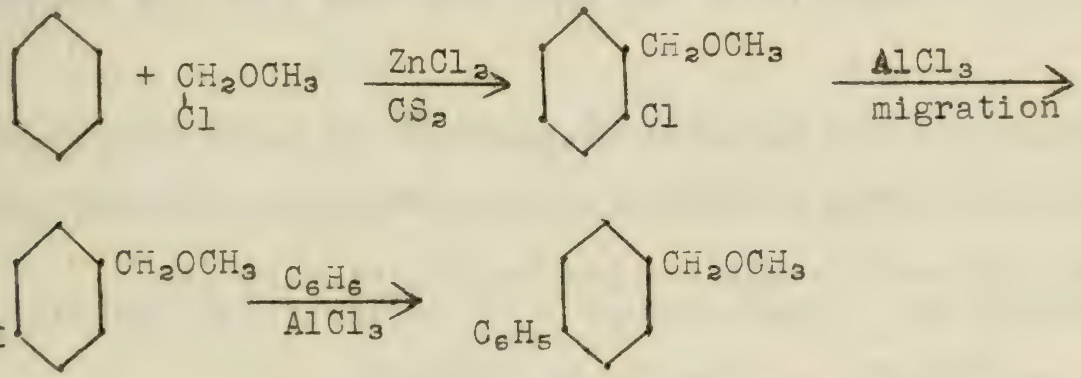


$$CH_3CH_2CH_2CH{=}CHCO_2H \xrightarrow[AlCl_3]{HCl} CH_3CH_2CH_2\underset{\displaystyle Cl}{\underset{|}{C}}HCH_2CO_2H \xrightarrow[migration]{AlCl_3}$$

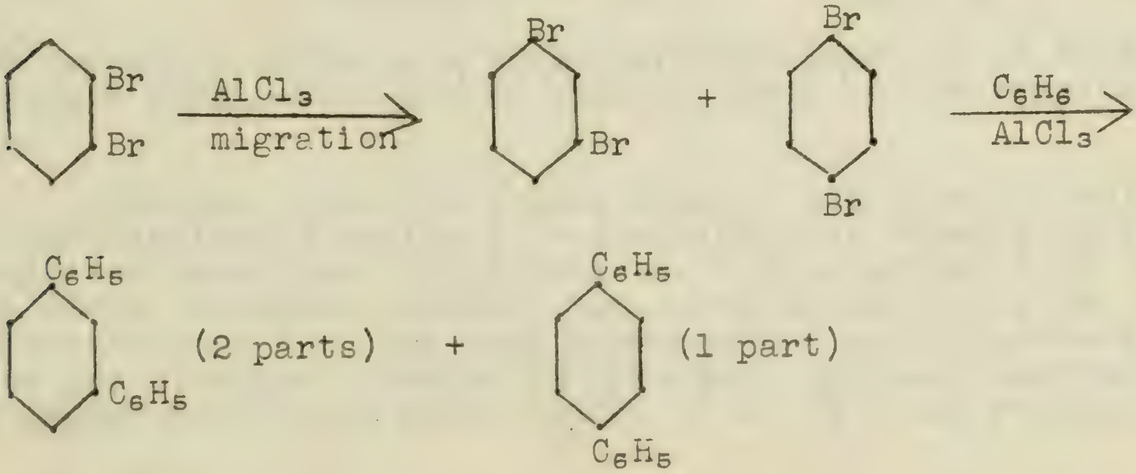
$$CH_3\underset{\displaystyle Cl}{\underset{|}{C}}HCH_2CH_2CH_2CO_2H \xrightarrow[AlCl_3]{C_6H_6} CH_3\underset{\displaystyle C_6H_5}{\underset{|}{C}}HCH_2CH_2CH_2CO_2H$$

This migration was explained by the nature of the complex formed between the carbonyl compound and aluminum chloride, in which the bonds are so loosened that an exchange in positions of atoms is possible. Under these conditions, the electronegative atoms, oxygen and chlorine, repel each other as far apart as possible. This hypothesis was strengthened by evidence which showed that the oxygen atom did not have to be in carbonyl linkage but that an oxygen atom in ether linkage exerted a repelling action on chlorine and furthermore, two adjacent halogen atoms behaved similarly, although with not as great a repulsion.

X

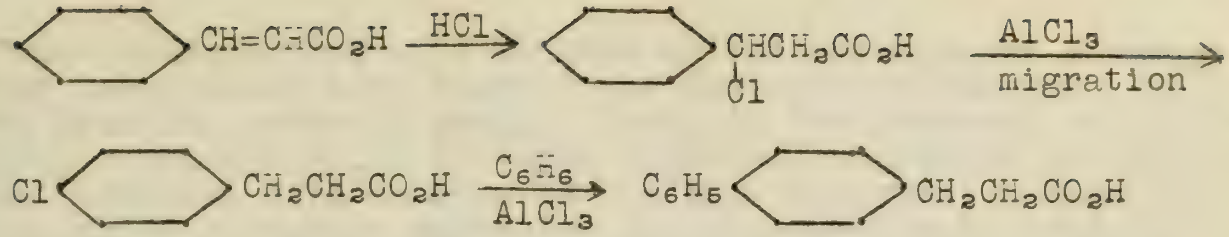


XI



With an oxygen atom in the side chain, the halogen atom migrated to the ring and as far away as possible from the side chain.

XII



To clear up this work, Nenitzescu, Gavat and Cocora investigated the action of aluminum chloride on an α,β-unsaturated acid in the absence of benzene, to find the hypothetical intermediate chloro-acid with the position of the chlorine changed. Accordingly, α,β-hexenoic acid was treated with aluminum chloride in carbon disulfide under mild conditions, and a large fraction of product was obtained, which, however, analyzed for only a small amount of chloro-acid. Isolation of this chloro-acid was hopeless, and all chlorine was removed by boiling with potassium hydroxide solution, leaving a hexenoic acid. This proved to consist chiefly of β,γ-hexenoic acid with a little of the γ,δ-acid. They postulated then that the migration of the double bond (and hence the migration of the halogen atoms observed before) was due to the alternate addition and splitting out of hydrogen chloride:

XIII

$$CH_3CH_2CH_2CH{=}CHCO_2H \rightleftharpoons CH_3CH_2CH_2CHClCH_2CO_2H \rightleftharpoons CH_3CH_2CH{=}CHCH_2CO_2H \rightleftharpoons$$

$$CH_3CH_2CHClCH_2CH_2CO_2H \rightleftharpoons CH_3CH{=}CHCH_2CH_2CO_2H \rightleftharpoons CH_3CHClCH_2CH_2CH_2CO_2H$$

This also explained why a halogen atom will not migrate to the terminal methyl group in a carbon chain. The reaction

$$CH_3CHCl- \rightarrow CH_2{=}CH \rightarrow CH_2ClCH_2-$$

is not probably, while in a true migration there is no reason why the halogen atom should not be shifted clear to the terminal methyl group.

The fact that the double bond in α,β-hexenoic acid does not shift quantitatively to the γ,δ-position, but chiefly only to the β,γ-position shows that the existence of this latter acid is favored by the above equilibria (XIII). At first glance, this is inconsistent with the fact that α.β-hexenoic acid condenses with benzene and aluminum chloride to give only δ-phenylcaproic acid.(IX). But a comparison of the reactivities of α-, β-, and γ-halogen acids

shows that condensation with benzene in the presence of aluminum chloride takes place more readily the farther the halogen atom is removed from the carboxyl group. Thus, in the presence of aluminum chloride, α-halogen acids in whose sturcture migration is impossible will not condense with benzene at its boiling point; β-halogen acids in whose structure migration is impossible will condense under these conditions, but not at room temperature; γ-acids will react at room temperature. The differences in reactivity of α-, β-, and γ-acids are so great in an equilibrium mixture of these halogenated acids, that practically the only acid to react with benzene is the one having the halogen farthest from the carboxyl group.

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January 15, 1941

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II Semester 1940-41

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THE WILLGERODT REACTION

Willgerodt - University of Leipzig   Fieser - Harvard
Bachmann - Michigan

C. Willgerodt, of the University of Leipzig, first noted in 1887 that alkyl aryl ketones undergo a remarkable reaction when heated with aqueous ammonium polysulfide (a solution of sulfur in aqueous ammonium sulfide), For example, acetophenone yields phenylacetamide and a smaller amount of the ammonium salt of phenylacetic acid. The reaction was studied by Willgerodt and his students over a period of many years and was found to be applicable not only to methyl ketones but also to ketones with side chains up to five or six carbon atoms long. In general the reaction can be formulated as follows:

$$\text{Aryl-CO}(CH_2)_nCH_3 \xrightarrow{NH_4S_x} \text{Aryl-}CH_2(CH_2)_nCONH_2$$

The alkyl side chain need not be straight. Thus, from phenyl isobutyl ketone it has been possible to obtain α-methyl-β-phenylbutyramide. In no case is there evidence that a rearrangement of the carbon chain occurs. The carbonyl group disappears and the terminal methyl group is converted into an amide or carboxyl salt group. The best yield reported by Willgerodt is for the case of acetophenone where 49.5 per cent of phenylacetamide and 13.5 per cent of ammonium phenylacetate, a total of 63 per cent, was obtained.

Only two references concerning the practical use of the Willgerodt reaction appeared in the literature from 1911 to 1940. Since neither of these reported good yields, the reaction was generally regarded as a chemical curiosity until last year, when it was "rediscovered" by two workers in the field of synthetic polycyclic hydrocarbons, Fieser of Harvard and Bachmann of Michigan. The simple modifications of using lower temperatures and a water-miscible organic solvent such as dioxane have made it possible to obtain good and sometimes almost quantitative yields of otherwise difficultly accessible intermediates. Inasmuch as the aryl-acetic, -propionic, and -butyric acids are frequently used in the synthesis of carcinogenic hydrocarbons and steroids, the Willgerodt reaction promises to become a useful synthetic tool, especially when its mechanism is better understood.

According to the usual procedure, as described by Fieser and by Bachmann, several grams of the ketone is heated eight to twelve hours with about five times its weight of ammonium polysulfide reagent in a sealed glass tube at 160-180°. The reagent is prepared by saturating concentrated ammonium hydroxide with hydrogen sulfide and dissolving 10 per cent by weight of sulfur in the solution. The addition of 40 per cent of dioxane greatly improves the yield. Usually the amide separates from the reaction mixture in crystalline form. If the acid is desired instead of the amide, it may be readily obtained by acid hydrolysis of the amide. Since the amides can usually be dehydrated to the nitriles without difficulty by means of

Willgerodt — University of [illegible]

[illegible]

C. Willgerodt, of the University of [illegible] [illegible]

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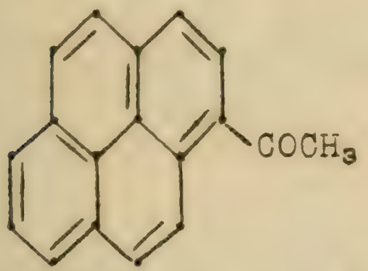
phosphorous pentoxide, this reaction provides a possible method for synthesizing these useful intermediates also.

The table on page 5 lists those ketones for which quantitative data regarding yields are available. In general it can be said that the yields are best for the methyl ketones. As the chain length increases the yields fall off rapidly until the reaction reaches a practical limit between the valeryl and heptyl ketones. Compounds with longer side chains appear to be cleaved, and the result is mainly resinification. Branching of the side chain also results in a sharp decrease in yield. The large aryl groups, such as pyrenyl, phenanthryl, and fluoryl, seem to react more smoothly than the smaller groups like naphthyl and phenyl. Polysubstituted aryl groups, such as mesityl and pseudocumyl, do not give good yields.

The most favorable cases yet studied are those of the 3-pyrenyl ketones:



$$\rightarrow C_{16}H_9-CH_2CONH_2 \xrightarrow[HOAc]{HCl} C_{16}H_9-CH_2COOH$$

(93%) (98% from amide)

$$C_{16}H_9-COCH_2CH_3 \rightarrow [C_{16}H_9-CH_2CH_2CONH_2] \rightarrow C_{16}H_9-CH_2COOH$$

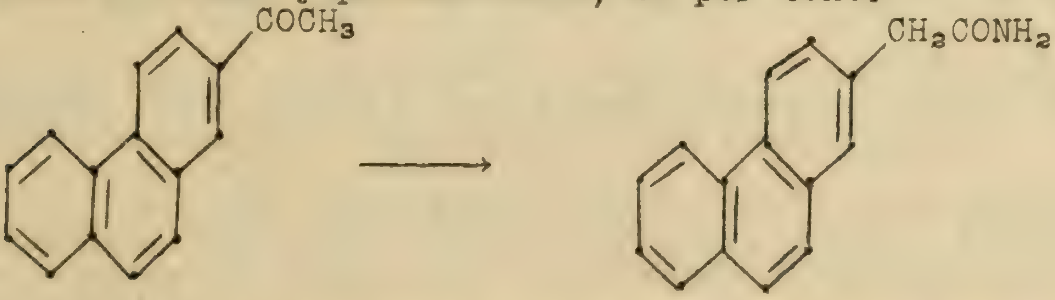
(67% from the ketone)

$$C_{16}H_9-COCH_2CH_2CH_3 \rightarrow [\text{Amide}] \rightarrow C_{16}H_9-CH_2CH_2CH_2COOH$$

(46% from the ketone)

The branched chain compounds, pyrenyl isopropyl ketone and pyrenyl isobutyl ketone, failed to yield crystalline amides.

The acetylphenanthrenes give good yields of amide - in the case of 2-acetylphenanthrene, 80 per cent.



2-Acetylfluorene yields 70 per cent of 2-fluoreneacetamide, which can be hydrolyzed practically quantitatively to form 2-fluoreneacetic acid, a substance which possesses plant hormone activity.

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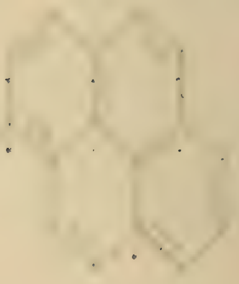

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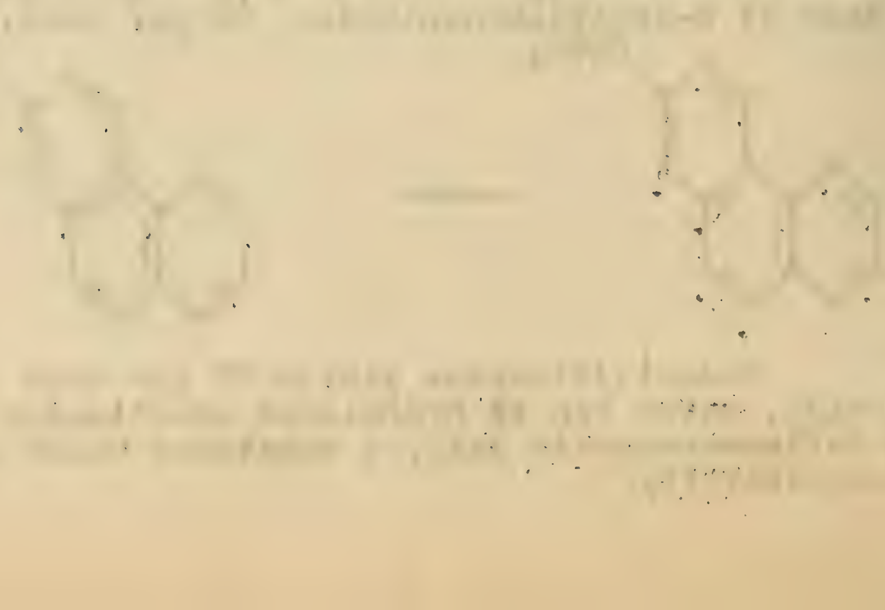

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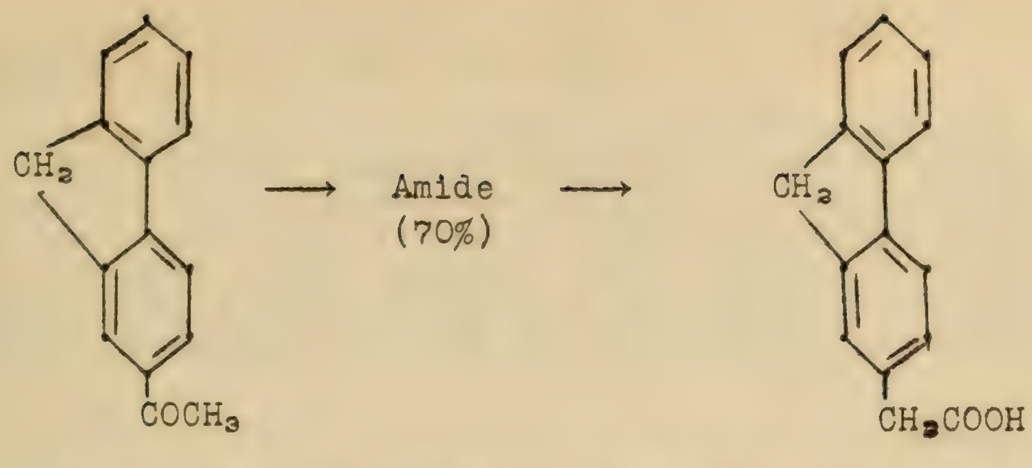
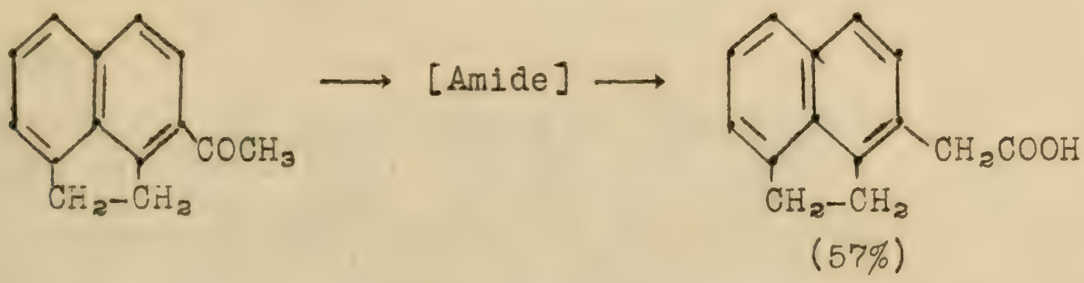
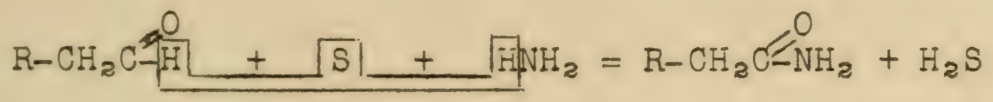


1-Acetylacenaphthene yields a crude amide from which an overall yield of 57 per cent of 1-acenaphthylacetic acid can be prepared:



Little is known of the mechanism of the Willgerodt reaction. In 1888 Willgerodt postulated that the oxygen atom of the carbonyl in some manner changes place with two hydrogen atoms of the terminal methyl group to form an aldehyde isomer of the ketone. This aldehyde is then converted to the amide by oxidizing action of the sulfur and ammonia:



$$R\text{-}CH_2\overset{O}{C}\text{-}\boxed{H} \quad + \quad \boxed{S} \quad + \quad \boxed{H}NH_2 = R\text{-}CH_2\overset{O}{C}\text{-}NH_2 + H_2S$$

The amide may undergo partial hydrolysis to form the ammonium salt of the corresponding acid.

In any attempt to evolve a satisfactory mechanism for this curious reaction, the following facts should be considered:

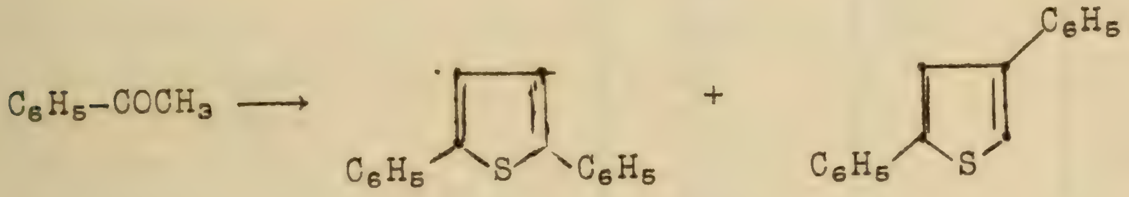
1. As a by-product, varying amounts of a hydrocarbon are isolated. This results from simple reduction of the carbonyl group; for example, ethylbenzene from acetophenone.

2. The final amide cannot result from oxidation of the hydrocarbon formed by reduction of the carbonyl, for hydrocarbons like toluene and xylene have been shown to be unaffected by the polysulfide reagent.

3. There is no evidence of the intermediate formation of a keto acid or keto amide which in turn could be reduced to the final product.

4. In no case does the reaction appear to involve a rearrangement of the carbon side chain.

5. Excess sulfur seems to be a necessary part of the reagent. If colorless ammonium sulfide is used in place of the yellow ammonium polysulfide, the yields fall off markedly, and at least in the case of certain methyl ketones another type of reaction accounts for most of the product. Thus, acetophenone with colorless ammonium sulfide yields 20 per cent of a mixture of isomeric disubstituted thiophenes in which the 2,5-diphenylthiophene predominates



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Reported by M. Carmack
February 5, 1941

Table of Yields in the Willgerodt Reaction

Ketone	Yield of Amide	Yield of acid (as ammonium salt)	Total Yield	Ref.
$C_6H_5\text{-}COCH_3$	49.6	13.5	63	4
$C_6H_5\text{-}COCH_2CH_3$	41	9.5	50.5	4
$C_6H_5\text{-}COCH_2CH_2CH_3$	32	5-6	37-38	4
$C_6H_5\text{-}COCH(CH_3)_2$	16	3	19	4
$C_6H_5\text{-}COCH_2CH(CH_3)_2$	14-15	2	16-17	4
$C_6H_5\text{-}CO(CH_2)_5CH_3$ [cleaved]	25 (heptanoic amide)			4
$\underline{p}\text{-}CH_3\text{-}C_6H_4\text{-}COCH_3$	45	8-10	53-55	5
$\underline{p}\text{-}CH_3\text{-}C_6H_4\text{-}COCH_2CH_3$	30	6-8	36-38	5
$\underline{p}\text{-}CH_3\text{-}C_6H_4\text{-}COCH_2CH_2CH_3$	18-20	5	23-25	5
$\underline{p}\text{-}CH_3\text{-}C_6H_4\text{-}COCH(CH_3)_2$	very small			5
$\underline{p}\text{-}CH_3\text{-}C_6H_4\text{-}COCH_2CH(CH_3)_2$	3-4		3-4	5
$\underline{p}\text{-}CH_3\text{-}C_6H_4\text{-}COCH_2CH_2CH_2CH_3$	2		2	5
α-Acetylnaphthalene	24	10	34	8
β-Acetylnaphthalene	13	10-12	23-25	8,3
1-Acetylacenaphthene		57	57	10
2-Acetylfluorene	70		70	11
2-Acetylphenanthrene	80-82		80-82	12
3-Acetylphenanthrene		68	68	12
3-Acetylpyrene	93		93	12
3-Pyrenyl-$COCH_2CH_3$		67 (from amide)	67	12
3-Pyrenyl-$COCH_2CH_2CH_3$		46 (from amide)	46	12

Many other ketones have been submitted to the Willgerodt reaction and products have been identified, but no quantitative data are available.

STUDIES ON THE WALDEN INVERSION

Winstein and Lucas, California Institute of Technology

Wilson and Lucas in 1936 discovered that when the isomeric 2-butenes underwent the series of reactions

butene → chlorohydrin → epoxide → glycol →

diacetate → dibromide → butene

pure cis-2-butene resulted in pure trans-2-butene, and vice versa. It is apparent that an odd number of Walden inversions have taken place.

At that time Lucas postulated that a series of five inversions had occurred, as follows:

(1) 2-butene $\xrightarrow[\text{W.I.}]{\text{HOCl}}$ 3-chloro-2-butanol

(2) 3-chloro-2-butanol $\xrightarrow[\text{W.I.}]{\text{KOH}}$ 2,3-epoxybutane

(3) 2,3-epoxybutane $\xrightarrow[\text{W.I.}]{H_2O}$ 2,3-butanediol

(4) 2,3-diacetoxybutane $\xrightarrow[\text{W.I.}]{\text{HBr}}$ 2,3-dibromobutane

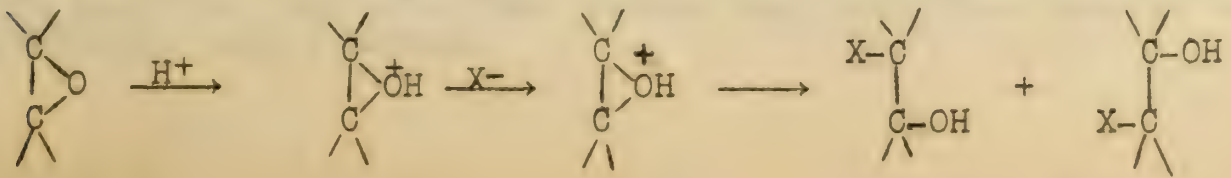
(5) 2,3-dibromobutane $\xrightarrow[\text{W.I.}]{\text{Zn}}$ 2-butene

Inversions (1) and (2) are well established by other work. It may be said in general that addition to double bonds and elimination occur trans.

Inversion (3) was demonstrated by means of optically active epoxides and glycols. The lower boiling epoxide was obtained in an active form from the corresponding dimethylcholine, which had been resolved with d-tartaric acid, and hence has the trans configuration. The other epoxide, boiling six degrees higher, is therefore the cis form.

The same relationship holds for the corresponding glycols, which are meso and racemic in configuration. dl-2,3-Butanediol (liquid) was resolved with d-camphorsulfonic acid and its configuration demonstrated. The other isomer (solid) is, of course, meso.

Since the known trans-epoxide (active) was converted into the meso-glycol and the cis-epoxide gave the dl-glycol on hydrolysis, it follows that inversion accompanied this reaction. No racemization occurred in either case. The mechanism postulated for trans opening of oxide rings is given here.



The reaction is catalyzed by acid, so the formation of the oxonium ion is reasonable. The negative ion X^- attacks this complex at the opposite face of either carbon atom, giving rise to two isomers.

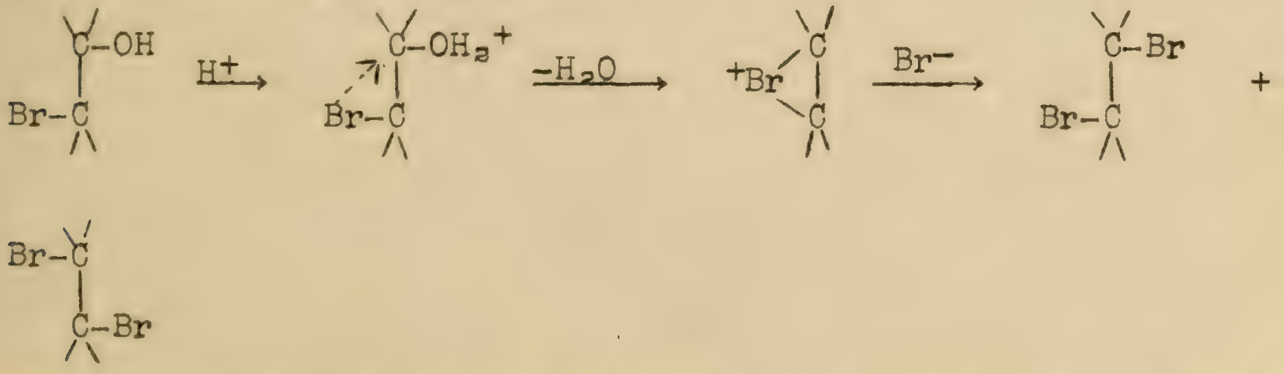
Inversion (4) was found, by neutralizing the reaction mixture and isolating intermediates, to involve four steps as follows:

$$\text{diacetate} \xrightarrow{H^+} \text{monoacetate} \xrightarrow[\text{W.I.}]{HBr} \text{acetate of bromohydrin} \xrightarrow{H^+} \text{bromohydrin} \xrightarrow{HBr} \text{dibromide}$$

The hydrolysis steps are known to occur without change in configuration since the assymetric carbon atoms are not involved. The last step has been shown to occur with complete retention of configuration. This is unusual, since most monohydric alcohols react similarly with racemization. The inversion, therefore, must accompany step two, the reaction of the monoacetate with HBr. Complete inversion here is also unusual, but must be the case since the whole process gives pure products and not mixtures. Apparently the presence of electron-attracting groups, ionizing solvents, and possible chelation favor a clean-cut inversion.

To establish the fact that the reaction of the 3-bromo-2-butanol with HBr is not accompanied by stereomutation, Winstein and Lucas prepared the pure threo- and erythro-3-bromo-2-butanols by the addition of HBr to pure cis- and trans-2,3-epoxybutane respectively. They found that the threo-bromohydrin, on treatment with HBr, formed the dl-dibromide and that the erythro isomer gave the meso-dibromide. The structures of the two dibromides are well known and a method of analysis of a mixture of the two was developed by Dillon, Young and Lucas in 1930.

The use of optically active bromohydrins and their acetates was valuable in developing a mechanism for this reaction. Both the active threo- and erythro-bromohydrins, as well as their acetates, resulted in inactive dibromides upon treatment with HBr. The mechanism proposed is



The bromonium complex in the case of the threo compound is inactive and hence the products are also. The negative bromine ion approaches the opposite side of either carbon atom and gives rise to two products, enantiomorphs.

Inversion (5) is accepted because of the general theory of *trans* elimination. It is definitely proved in this case since the configurations of both dibromides and both butenes are well established.

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Reported by W. D. McPhee
February 5, 1941

SOME APPLICATIONS OF POLAROGRAPHY IN ORGANIC CHEMISTRY

I PRINCIPLE

The polarographic method of chemical analysis is based on the interpretation of current-voltage curves obtained by electrolyzing solutions of electroreducible or electrooxidizable substances in a cell in which one electrode consists of mercury falling slowly in small drops from a capillary tube. Strictly speaking, one should use the term voltarimetry or amperometric titration for this method of analysis, but the term polarography is more commonly used. From the current-voltage curves both the species and concentration of the electrolyzed substance can be determined, and under optimum conditions it is possible to detect and determine several substances simultaneously from a single c.v. curve. The method is especially suitable for small concentration (10^{-5} to 10^{-2} molar), and the electrolysis can be carried out with a volume of solution as small as 0.1 cc. Another virtue of the method is that the electrolyzed solution remains virtually unchanged since the current which passes through the solution is very small. Thus the material can be reclaimed after a determination.

A typical c.v. curve is shown in figure 1. Only an exceedingly small current, the "residual current", flows through the cell until the decomposition potential (point A) is reached. When this potential is exceeded continuous electrolysis begins. The current does not increase indefinitely with increasing applied E.M.F., but gradually approaches a limiting value and finally becomes constant (point C) and independent of further increase in applied E.M.F. Under optimum conditions, and with all other factors constant, the limiting current is directly proportional to the concentration of the electroreducible substance. This is the basis of quantitative polarography.

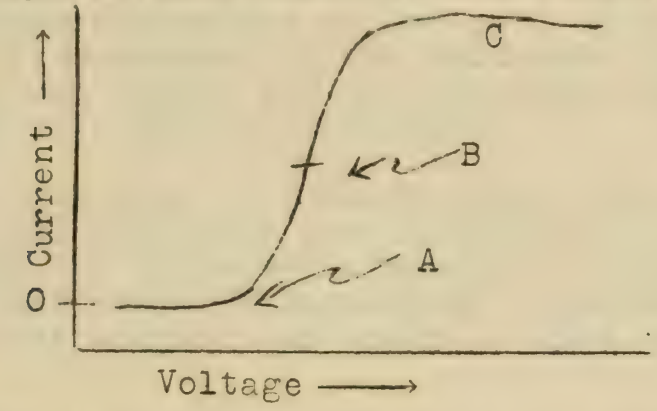

Figure 1.

The limiting current is produced by an extreme state of concentration polarization at the dropping electrode. As a result of the discharge process, the concentration of the reducible material is depleted close to the surface of the dropping electrode. This deficiency is compensated by diffusion of a fresh supply of reducible material from the body of the solution. The rate of diffusion depends directly on the concentration gradient

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between the surface of the electrode and the bulk of the solution. As the E.M.F. is increased above the decomposition potential the current increases and the average concentration at the surface of the electrode decreases, causing a corresponding increase in the rate of diffusion. Eventually the concentration at the surface of the mercury drop becomes so small compared to the concentration in the body of the solution the difference in concentration approaches a constant average value, equal simply to the concentration in the solution. Therefore the rate of diffusion also becomes constant. Beyond this point the amount of material discharging, and therefore the current, becomes constant and virtually independent of further increase in applied E.M.F. Since the rate of diffusion reaches a constant value which is directly proportional to the concentration in the solution the quantitative principle of polarography is apparent.

The "half-wave potential" (point B, fig.1) is characteristi of the particular electroreducible substance. As the name implies it is the value of the potential of the dropping electrode against an external reference electrode, at that point on the current-voltage curve where the current equals one-half its limiting value. Qualitative polarographic analysis is based on the characterization of the half-wave potentials on the c.v. curves of "unknown" solutions. By comparison of the half-wave potential on "unknown" curves with known values for various materials, the substance producing the wave can be identified.

When several electroreducible substances are present in a solution, each will give its characteristic wave on the c.v. curve provided the half-wave potentials of the substances are sufficiently different in magnitude. Generally this difference must be at least 0.2 volt in order to give separate and distinct waves.

Current voltage waves do not always have the "ideal" shape shown in figure 1, but are sometimes distorted by maxima. The curve rises sharply until a certain potential is reached, and then falls rather rapidly towards a limiting value.

Since most reductions of organic compounds are irreversible or at least involve irreversible steps, it is not surprising that much less is known of the interpretation of c.v. curves of organic compounds than of most inorganic compounds. In most of the older work "reduction potentials" and not half-wave potentials were determined and reported. These "reduction potentials" were derived from the polarograms by different conventional methods. The principle shortcomings of these methods are that these potentials change with the concentration of the electroreducible substance, with the sensitivity of the galvanometer, and with the drop time and the rate of flow of mercury.

between the surface of the electrode and the bulk of the solution. As the E.M.F. is increased above the decomposition potential the current increases and the average concentration of the reducible the electrode interface, causing a corresponding increase in the rate of diffusion. Eventually the concentration at the surface of the electrode becomes so small compared to the concentration in the body of the solution the difference in concentration approaches a constant average value, equal simply to the concentration in the solution. Therefore the rate of diffusion reaches a maximum value, beyond this point the amount of material diffusing, and therefore the current, becomes constant and virtually independent of further increase in applied E.M.F. Since the rate of diffusion reaches a constant value which is directly proportional to the concentration in the solution the quantitative principle of polarography is apparent.

The "half-wave potential" (point D, (Fig.) is characteristic of the particular electroreducible substance. As the name implies it is the value of the potential of the dropping electrode against an external reference electrode, at that point on the current-voltage curve where the current equals one-half its limiting value. Qualitative polarographic analysis is based on the characteristics of the half-wave potentials of the c.v. curves of "unknown" solutions. By comparison of the half-wave potential of "unknown" curves with known values for various materials, the substance producing the wave can be identified.

When several electroreducible substances are present in a solution, each will give its characteristic wave on the c.v. curve provided the half-wave potentials of the substances are sufficiently different in magnitude. Generally this difference must be at least 0.2 volt if they are to give well defined waves.

Current voltage curves do not always have the "ideal" shape shown in Figure 1, but are sometimes distorted by maxima. The curves rise sharply until a certain point is reached, and then fall either gradually towards a limiting value.

Since small concentrations of organic compounds are frequently are at least invariably present in these studies, it is not surprising that much work is being done on the interpretation of c.v. curves of organic compounds. In most of the older work "half-wave potentials" and not polarographic data were determined and reported. These "polarographic constants" were derived from the polarograms by different experimental methods. The principal drawbacks of these methods are that half-wave potentials change with the concentration of the electroreducible substance, with the pH of the solution, and with the drop time and the rate of flow of mercury.

Since there is such a lack of uniformity in the methods of reporting data on organic compounds it has been recommended that in the future the following data be reported:

(1) Concentration of suitable agents used to eliminate maxima.

(2) Half-wave potentials and their dependence on concentration, pH, and the medium.

(3) Equation of the wave.

(4) Number of electrons involved in the reduction.

(5) The effect of pH (buffer solutions are required).

(6) The effect of the medium (the pH of an aqueous buffer is affected by an organic solvent.

(7) Range in which the diffusion current is directly proportional to the concentration. If such a range is not found a calibration curve has to be made for analytical purposes.

(8) Effect of cations and anions on half-wave potentials.

(9) Number of hydrogen ions participating in the electroreduction.

(10) Reduction potentials obtained by conventional methods in cases in which waves are drawn out.

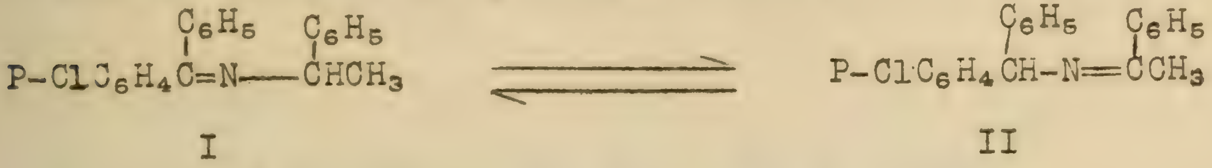
It is only by rigorous fulfillment of these requirements that the full value of the polarograph as tool in organic chemistry can be realized. Entirely too much of the earlier and contemporary work has been done under varying and undefined conditions.

II Applications

The first organic substance to be reduced at the dropping mercury cathode was nitrobenzene. This reduction was studied in 1925 by Shikata. Since that time more than three hundred organic compounds have been studied polarographically. However, the difficulties encountered were far greater than in inorganic reduction.

In addition to qualitative and quantitative analyses, the polarographic method may be used in studies of the influence of substituted groups and of conjugation on the reduction potential, in examinations of organic reactions such as complex formation, tautomerism, and polymerization, and in investigations of the nature of processes at the electrode surface.

A very striking example of the reliability of polarographic analysis is the work of Borchert and Adkins who studied the rate of tautomerization of an optically active azomethine (I).



$$P\text{-}ClC_6H_4\overset{C_6H_5}{C}{=}N\text{—}\overset{C_6H_5}{C}HCH_3 \rightleftharpoons P\text{-}ClC_6H_4\overset{C_6H_5}{C}H\text{-}N{=}\overset{C_6H_5}{C}CH_3$$

I II

The dropping mercury cathode was used to quantitatively analyze the mixture of ketones obtained by hydrolysis of the components.

Adkins et al have also used the polarograph to determine the concentrations at equilibrium of the ketones in the systems of the type

$$R_2CO + R'_2CHOH \rightleftharpoons R_2CHOH + R'_2CO$$

From the equilibrium concentrations the relative strength as oxidizing agents of the ketones was determined.

Cantor and Peniston have studied the reduction of aldoses at the dropping mercury electrode to determine the concentration of the free aldehyde form in sugar solutions.

Kerr has devised a method for estimating dextrose in starch conversions which agrees closely with the slower gravimetric method.

The polarographic analysis of mixtures of aldehydes and peroxides has been carried out by Stern and Polak and by Gosman.

Schwaer has studied the electroreduction of some unsaturate acids. In general unsaturated acids with conjugated double bonds are easily reducible both in acid and alkaline solution. A clear demonstration of the selectivity of electroreduction is found in the fact that one can distinguish between cis and trans isomeric acids if the determination is made in alkaline solution.

Cope and Hardy have used the polarograph to analyze mixture of α-β and β-γ unsaturated isomeric esters. The α-β unsaturated esters are electroreducible, whereas the β-γ unsaturated esters are not.

The polarographic determination of certain natural products has been reported by Hershberg, Wolfe, and Fieser. Ketosteroids, non-ketonic alcohols of the sterol group, vitamin K_1, and heart poisons have been examined.

A study of the keto-enol tautomerism of the pyruvate ion was made by Muller and Baumberger. These workers carried out the electroreductions at varying pH values and found evidence for two distinctly different substances in equilibrium. The same workers also studied the polymerization of the pyruvate ion.

Scores of other organic compounds have been studied polarographically, and a list of these complete to June, 1938 is contained in a review article by Muller.

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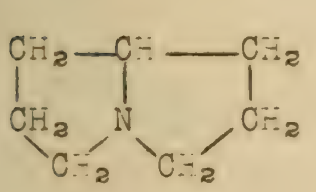
Reported by D. J. Byers
February 12, 1941

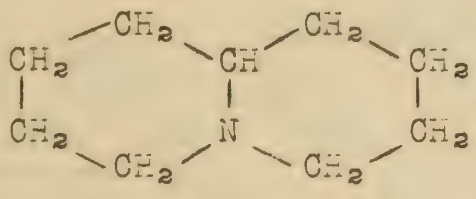
BICYCLOAZA ALKANES

Vlado Prelog et al, University of Zagreb, Yugoslavia

Bicyclic structures containing nitrogen as one of the uniting atoms have been of interest because of their occurrence in natural products. The pyrrolizidine structure (I) occurs in the Crotalaria, Heliotropium, Senecio, and Trichodesma alkaloids, the norlupinane structure (II) is present in the alkaloids of broom and lupin, and quinuclidine nucleus (III) is present in the important cinchona alkaloids.



I



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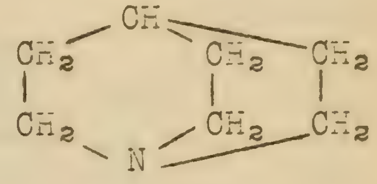
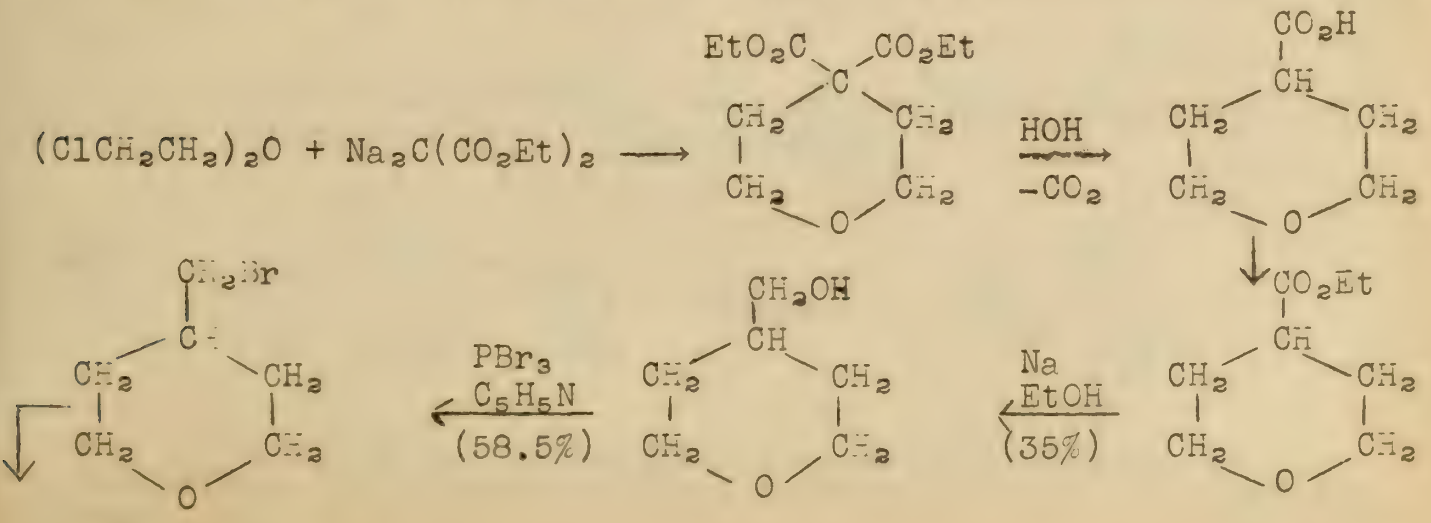


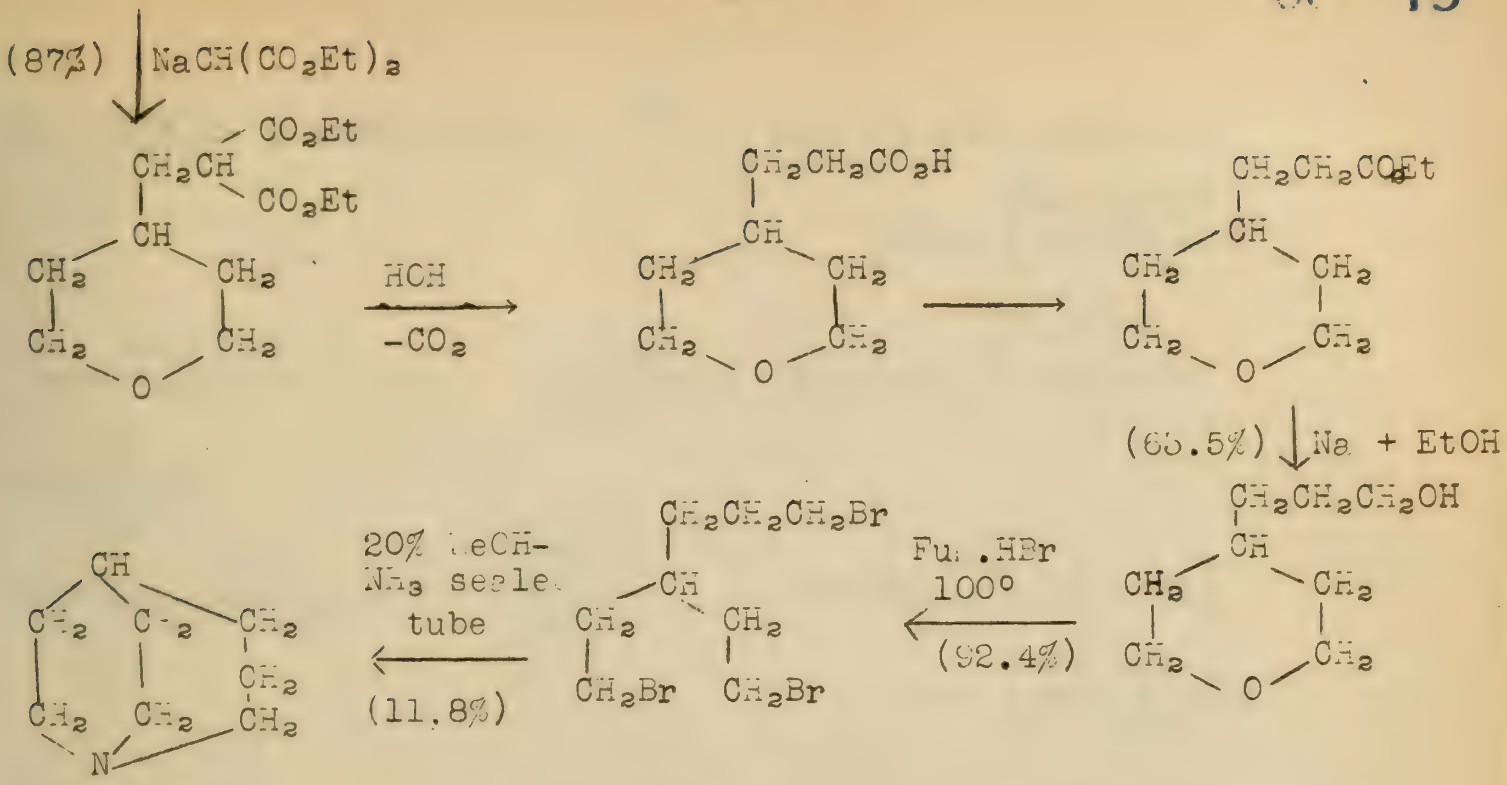
III

The general approach to the syntheses of these bicycloaza compounds has been to start with a heteromonocyclic compound, substitute the appropriate groups into the ring, and then close the second ring, usually by an intramolecular alkylation or by the Dieckmann reaction. One limitation to this attack is the difficulty of obtaining many of the starting materials. If pyridine is used as as a starting material, then one of the rings must be six-membered. The Dieckmann reaction is usually used only for 5- and 6-membered rings, and it fails when the 1,3-positions in a ring are to be linked.

Prelog and his coworkers have recently developed a method of forming these bicyclic bases by two-fold intramolecular alkylations. The starting materials are aliphatic compounds and the two rings are closed in a single operation, using Ruggli's high dilution principle.

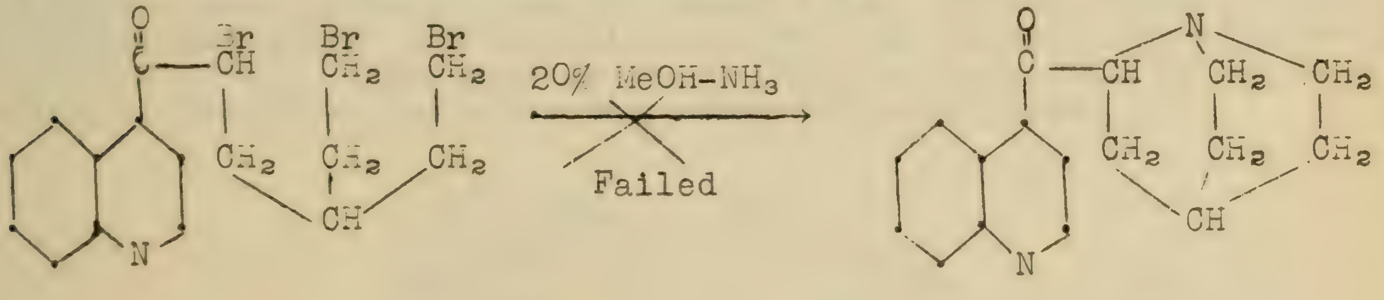
In his earlier work Prelog synthesized aliphatic tribromo derivatives and closed the rings by heating these with ammonia. This method has been useful, but its applications are limited. It may be illustrated by the synthesis of bicyclo-[3,2,2]-aza-1-nonane (IV):





IV

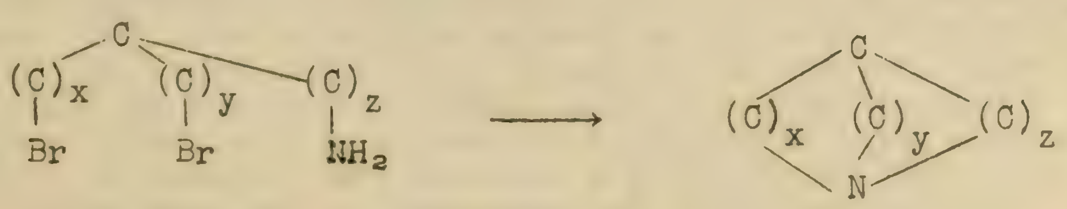
This method has also been successfully applied to the syntheses of quinuclidine, quinuclidine-2-carboxylic acid, bicyclo-[2,2,1]-aza-1-heptane, 7-methylbicyclo-[2,2,1]-aza-1-heptane, and 7-ethylbicyclo-[2,2,1]-aza-1-heptane. It will not work to make bicyclo-[3,3,1]-aza-1-nonane from 1,7-dibromo-4-(bromomethyl)-heptane, and an attempt to prepare a quinine-like compound, rubanone-9 (VI), from the tribromo derivative (V) was not successful.



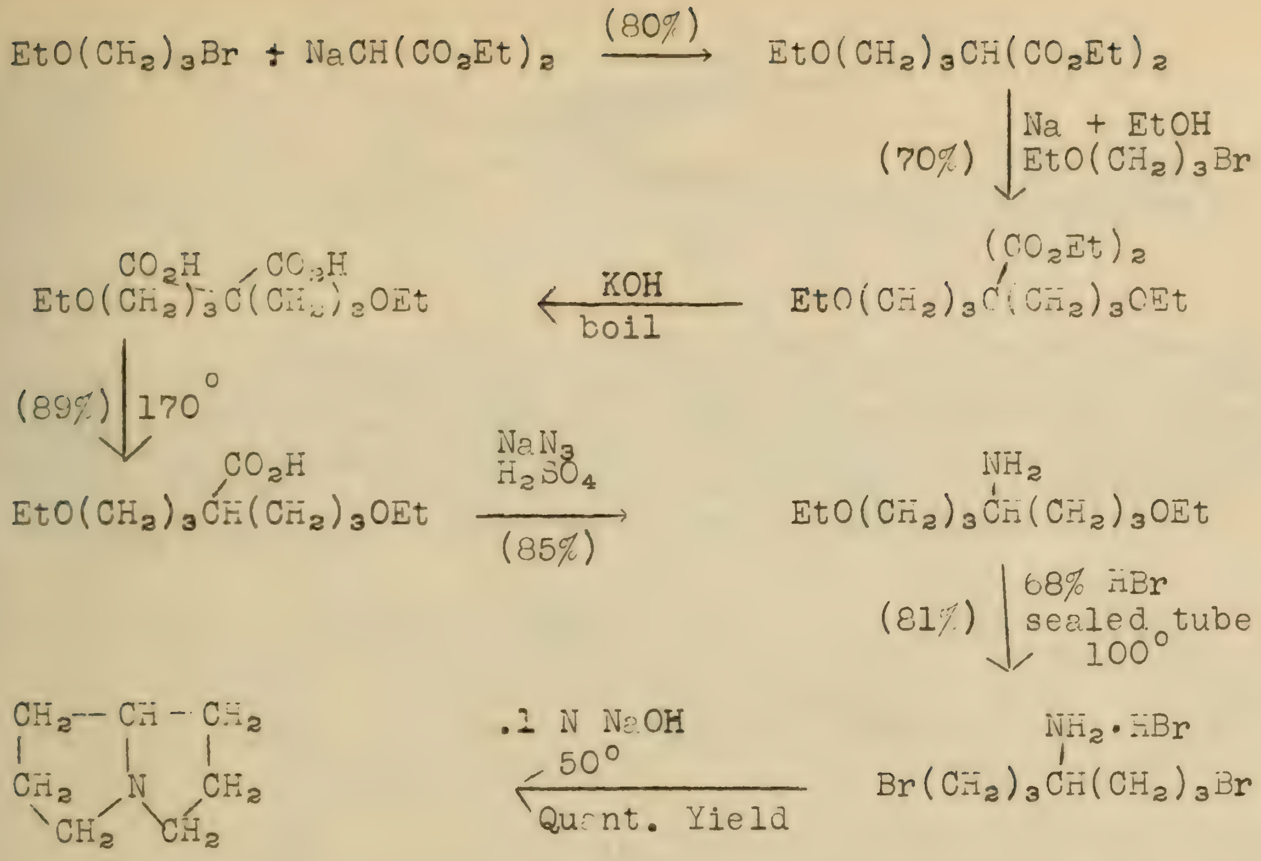
V

VI

More recently Prelog has employed dibromoamino compounds as starting materials for the ring closures:

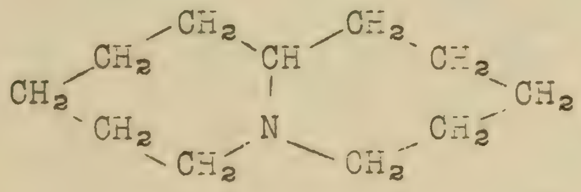


Thus, he has synthesized the hitherto unprepared pyrrolizidine (bicyclo-[3,3,0]-aza-1-octane) (I) by the following steps:



I

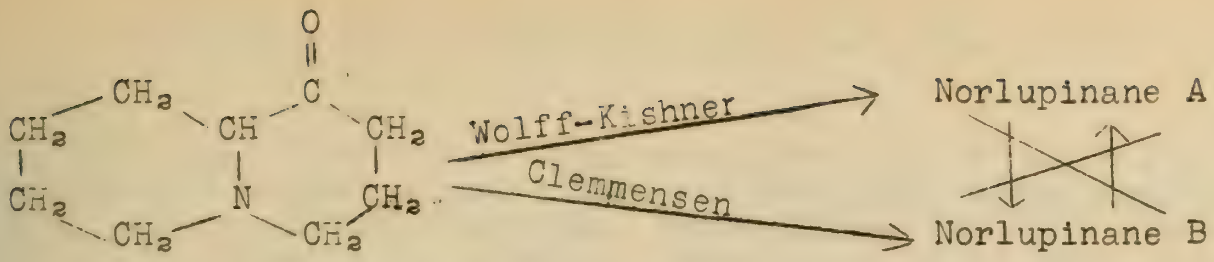
Other compounds which have been prepared by analogous procedures are norlupinane (bicyclo-[4,4,0]-aza-1-decane)(II), quinuclidine, 7-ethylbicyclo-[2,2,1]-aza-1-heptane, 7,7-dimethylbicyclo-[2,2,1]-aza-1-heptane, 2-methylquinuclidine, 2-ethylquinuclidine, 3-methylquinuclidine, 3-ethylquinuclidine, and bicyclo-[5,5,0]-aza-1-dodecane (VII). This last compound (VII) is particularly interesting since it contains two condensed seven-membered rings.



VII

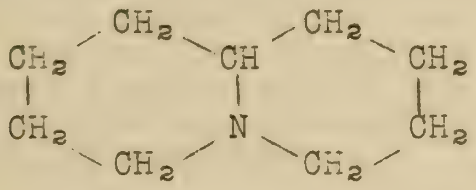
Norlupinanes A and B:

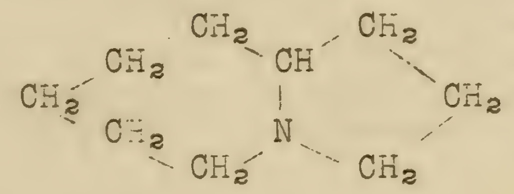
The syntheses of norlupinane (II) and of bicyclo-[5,3,0]-aza-1-decane (IX) have served to correct a misconception in the chemistry of the lupin alkaloids. Clemo et al reduced 1-ketonorlupinane (VIII) by the Wolff-Kishner method to norlupinane A (II) and by Clemmensen reduction to an isomer of II, which they called norlupinane B. They considered norlupinanes A and B to be cis-trans isomers analogous to the decalins. They were not interconvertible.



VIII

Prelog synthesized bicyclo-[0,4,4,]-aza-1-decane (II) and found it to be identical with norlupinane A. He then synthesized bicyclo-[5,3,0]-aza-1-decane, (IX), which turned out to be identical with norlupinane B. Thus the two products of reduction of 1-ketonorlupinane (VIII) are not geometrical, but structural, isomers, as the Clemmensen reduction caused a rearrangement.





II Norlupinane A

IX So-called Norlupinane B

Other Applications

Prelog has also applied two-fold intramolecular alkylations to the formation of bicyclothianium salts, in which the hetero atom is sulfur.

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V. Prelog et al, Ann. 525, 292 (1936); 532, 69, 83 (1937); 535, 37 (1938); 537, 214 (1939); 545, 229, 231, 243, 247, 256, 259 (1940); Ber., 72B, 672, 1101, 1103, 1319, 1325, 1638 (1939); J. Chem. Soc., 1938, 400; 1939, 677; C.A. 30, 1376 (1936); 10, 399 (1938); 33, 599 (1939); Coll. Czechoslav. Chem. Comm., 7, 430 (1935); 4, 259 (1932); C.A. 26, 5302 (1932); Archiv. Hem. i Tehnol. 13, 97 (1939); C.A. 34, 6296 (1940).

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Reported by Robert L. Frank
February 12, 1941

THE ACTION OF INVERT-SOAPS ON CELLULAR PROTEINS

Richard Kuhn - Kaiser-Wilhelm Institute of Medicine

The name "Invert-Soap" has been given to certain quaternary ammonium and sulfonium salts that contain large alkyl radicals in the cation portion of the molecule. These differ from the ordinary fatty acid salts, wherein the strongly hydrophobic alkyl group is in the anion. Invert-soaps resemble ordinary soaps in that their water solutions are foamy.

Bactericidal action, exhibited by certain of these quaternary ammonium salts, was observed by G. Domagk in 1935. An example of a disinfectant, known as "Zephirol," consisted of a mixture of alkyl-dimethyl-benzyl-ammoniumchlorides, where the alkyl groups contained 8, 10, 12, 14, 16 and 18 carbon atoms in straight chains.

Kuhn and his collaborators have undertaken the job of gaining some insight concerning the nature of this disinfectant action. The attempt has been made to correlate some physical and structural properties of these compounds with the effectiveness of disinfection; and the results of treating several types of protein complexes with invert-soaps were studied.

Five groups of invert-soaps were studied. The general methods of preparation, physical properties, comparison of structure, etc., of each group will be discussed, and will be followed by quantitative data on the minimum concentrations necessary for complete bactericidal action on standard cultures. Finally, the effect of invert-soaps on protein complexes will be reviewed.

Group I Dialkyl-methyl-benzyl-ammoniumchlorides

These salts were prepared by heating the methyldialkylamines with benzylchloride at 110° for varying lengths of time (1/4 hour to 12 hours). The mixtures became turbid, oils separated, and the salts were usually crystallized from alcohol-acetic acid mixtures. Yields were nearly quantitative for the dibutyl-, dihexyl-, dioctyl-, dilauryl- and dicetylmethylbenzylammoniumchloride.

For these, and later compounds, the lowering of the surface tension of water solutions was measured by a stalagmometer. The surface tension varied inversely as the number of drops of solution falling from an opening of given size. In Figure 1, the drop number is plotted against the number of carbon atoms in the alkyl groups, using a 0.01% solution of the invert soaps.

The bactericidal action on streptbacteria parallels the drop number curve, both reaching a maximum for the dilauryl compound. The dibutyl, dihexyl, and dicetyl compounds were relatively noneffective.

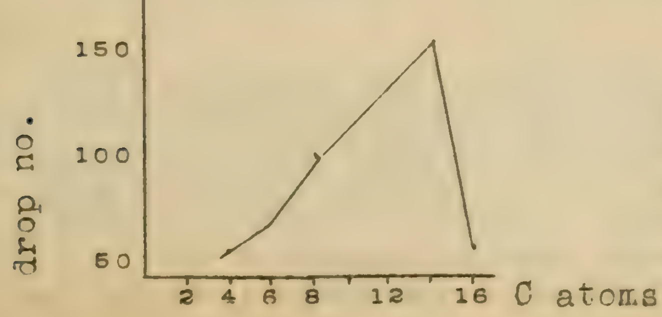


Figure 1

The monolauryl-dimethyl-benzylammoniumchloride compound was about one-fourth as active as the dilauryl compound. For other bacteria, the effectiveness of the dilauryl and dioctyl compounds was reversed. (Table 1)

Group II Butyl-, octyl-, lauryl-, and cetyldimethylsulfonium iodide.

The general preparation is indicated as follows:

$$CH_3SH + C_2H_5ONa \xrightarrow{-10^{\circ}} CH_3SNa + C_2H_5OH$$

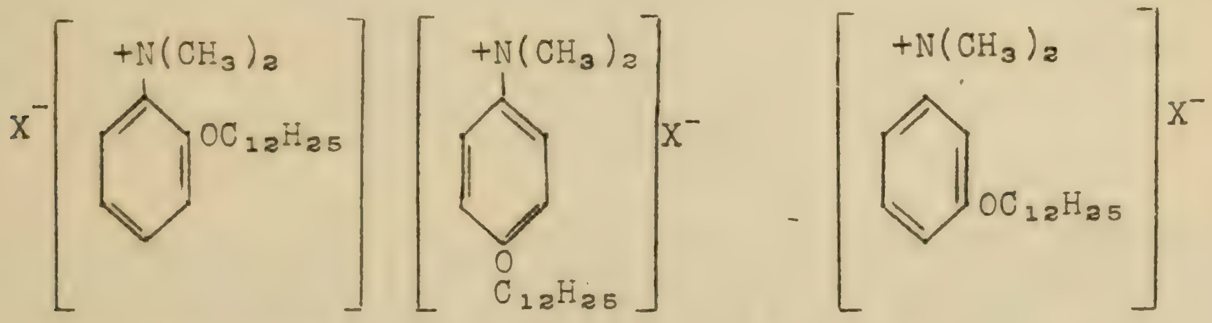
$$CH_3SNa + R\text{-}Br \rightarrow CH_3\text{-}S\text{-}R + NaBr$$

$$CH_3\text{-}S\text{-}R + CH_3I \rightarrow [(CH_3)_2RS]^{+}I^{-}$$

The salts were deliquescent and reactions were carried out under dry nitrogen. Yields were nearly quantitative. In this series, the drop numbers increase for an increase in the size of R groups in 2% solutions. From Table 2 it is seen that bactericidal action on staphylococci increases with the size of the alkyl group, but on coli, the maximum is reached for the lauryl compound. Quantitatively, the bactericidal action of sulfonium salts is weaker than that of the quaternary ammonium salts. The variations of minimum concentrations necessary to kill different types of bacteria may depend on the specific protein or complex present in the cells.

Group III Quaternary salts of aminophenyl ethers

The three compounds shown were made from the corresponding nitrophenols, by conversion to the potassium phenolates and subsequent reaction with lauryl chloride. This was followed by reduction with hydrogen, and finally, treatment with dimethylsulfate.



$X = [CH_3\text{-}OSO_3]^{-}$

Overall yields were about 40%, and the meta compound was obtained from commercially available m-dimethylaminophenol. In this series, the ortho compound lowered the surface tension of water the most, and the para compound lowered it the least. The ortho compound was more effective on several bacteria, but the usual exceptions appear in Table 3. The distance between the lauryl group and the positive charge varied in these compounds, and this was considered as influential.

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CASE II [illegible]

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[illegible]

CASE III Substituted salts of [illegible]

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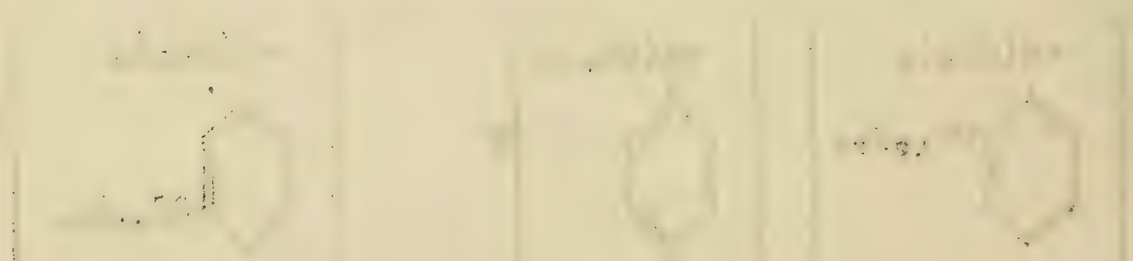

3 - [illegible]

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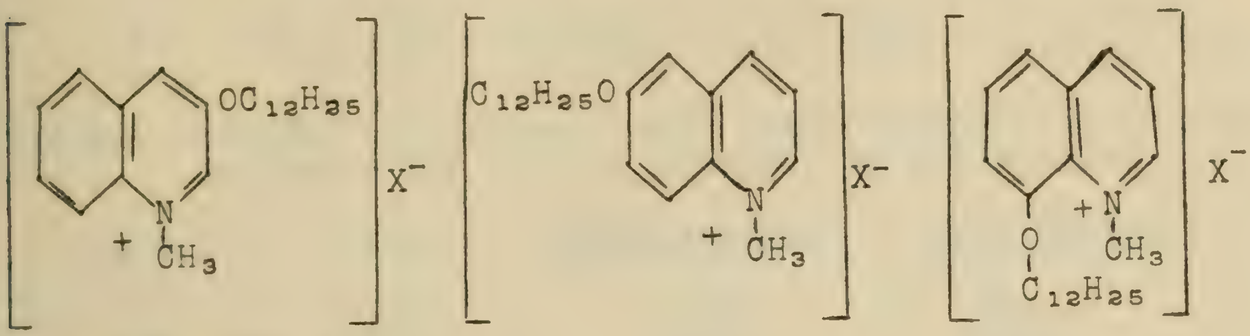
Group IV Quaternary salts of isomeric alkylquinoline ethers

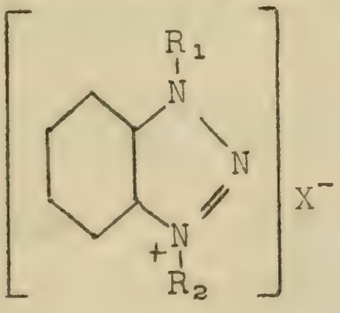
A typical preparation of these compounds involved the reaction of the corresponding hydroxyquinoline with lauryl chloride in the presence of potassium ethylate. The resulting ethers were treated with dimethylsulfate to yield the salts. One per cent solutions of the 3, 6 and 8 position isomers had drop number values of 89, 84 and 76, respectively. As in the previous series, there was no complete correlation between the one exhibiting the greater surface tension lowering being the most effective bactericidal. See Table 4.



$X^- = [CH_3\text{-}OSO_3]^-$

Group V Triazolium salts

In the benzotriazole series, benzotriazole is made from o-phenylenediamine and nitrous acid. The acidic hydrogen can be replaced by an alkyl group, and any salt may be obtained by adding the proper alkyl halide or dialkyl sulfate. The general type formula is:



For the cases where $R_1 = R_2$, the diethyl, dibutyl and dibenzyl compounds were relatively ineffective; and the dioctyl compound was from three to twenty times as effective as the dilauryl compound. (See Table 5.) On the other hand, where $R_1 \neq R_2$, the 1-lauryl-3-ethylbenzotriazolium bromide was the most effective of the different "mixed" combinations tested.

The compound 1-lauryl-4-ethyltriazolium bromide was prepared and tested, but was found not to be as effective as most of the benzotriazolium salts.

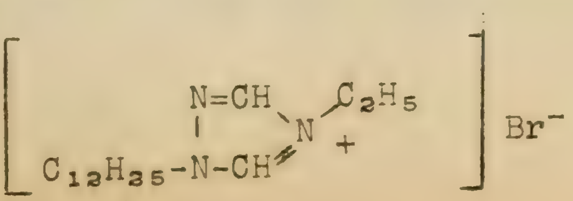


Table 1. Minimum Concentrations of Dialkyl-methyl-benzylammonium-chlorides for Killing Bacteria in 10 Minutes.

Alkyl	Staph.	Coli	Diphth.	Strept.*
C_8	1:38,400	1:25,600	1:51,200	1:400,000
C_{12}	1:4,800	1:6,400	1:25,600	1:1,600,000

*No time limit

Table 2. Minimum Concentrations of Alkyldimethylsulfoniumiodides Necessary for Killing Bacteria in 2.5 Minutes.

Alkyl	Coli	Staphylococci	Drop Number
C_4	1:50	1:50	44.5
C_8	1:50	1:50	59.0
C_{12}	1:1000	1:500	98.5
C_{16}	1:200	1:5000	--

Table 3. Minimum Concentrations of Quaternary Salts of Phenyl Ethers Necessary to Kill Bacteria in 10 Minutes.

Compd.	Staph.	Coli	Diphth.	Strept.
O	1:4800	1:6400	1:2400	1:25,600
m	1:4800	1:12,800	1:1600	1:12,800
p	1:1600	1:6400	1:2400	1:76,800
*Std.	1:1200	1:9600	1:4800	1:19,200

*Std. = lauryldimethylammoniumbromide

Table 4. Minimum Concentrations of Salts of Quinoline Ethers Necessary to Kill Bacteria in 10 Minutes.

Isomer	Staph.	Diphth.	Coli
3	1:1200	1:9600	1:9600
6	1:4800	1:2400	1:19,200
8	1:4800	1:3200	1:6400

Table 5. Minimum Concentrations of Benzotriazolium Salts Necessary to Kill Bacteria in 10 Minutes.

Compound	Staph.	Coli	Diphth.	Strept.
$R_1 = R_2 = C_8$	1:76,800	1:51,200	1:76,800	1:51,200
$R_1 = R_2 = C_{12}$	1:4800	1:3200	1:19,200	---
$R_1 = C_{12}$; $R_2 = C_2$	1:615,000	1:205,000	1:615,000	1:307,200
$R_1 = C_{16}$; $R_2 = C_2$	1:38,400	1:6400	1:76,800	1:38,400

The effect of lauryldimethylbenzylammoniumbromide on different types of proteins and protein complexes was studied with the idea of shedding some light on the bactericidal action of invert-soaps.

The first group, called "symplexes," were protein substances to which some colored prosthetic group was attached. From the eggs of certain sea urchins, a red-violet npahthoquinone dye was set free from the protein component by addition of a dilute solution of the invert-soap, provided the pH was controlled. Otherwise, the protein complex was merely precipitated from which the dye could not be extracted.

By treating an aqueous solution of chloroplast, obtained from fresh green leaves, with a dilute solution of invert-soap, all of the colored material could be extracted with benzene or ether. The optimum concentration for this cleaving corresponded with the concentration showing greatest ability to lower the surface tension of the solution.

Carotin exists as a prosthetic group in a protein symplex in raw carrots. On precipitating the protein component with invert-soap solution, the carotin is set free and can be extracted. Thus it was suggested that this method be adopted for quantitative determinations of chlorophyll and carotin, since it eliminated the necessity of drying, etc. for long periods of time.

In contrast to the above "symplexes," true chromoproteins are not cleaved by treatment with invert-soaps. A pure yellow enzyme from yeast can be precipitated by heat treatment, but addition of invert-soaps retards this coagulation, and does not cleave the lactoflavin from the protein component. Similarly, samples of oxyhemoglobin were unaffected by invert-soap treatment, and the iron-porphyrin complex precipitated with the protein on heat treatment alone. On other chromoproteins, invert-soaps did precipitate varying amounts of the substances, depending on the concentration of the invert soap.

In the case of simple proteins, such as egg albumen or gelatin, invert soaps cause precipitation, whereas none occurs in the case of globin or insulin. This difference seems to depend on the iso-electric points of the different substances, so that for example, a strongly basic protein is precipitated in a soda solution.

When small concentrations of invert-soap are used on egg albumen (1:15,000) no precipitation results, but rather a chemical change occurs, involving the setting free of an -SH group.

It is observed that, in general the comparison of concentrations of invert-soaps necessary for killing bacteria with that necessary for cleaving symplexes or precipitating proteins is of the order of 1:1000 - 1:50,000. The conclusion is that there is some relationship present between the two phenomena, and the theory of disinfectant action might rest with the reaction of invert-soaps with the cell protein of the bacteria.

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R. Kuhn, D. Jerchel and O. Westphal, *ibid.*, 73, 1095 (1940).
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Reported by James A. Robertson
February 19, 1941

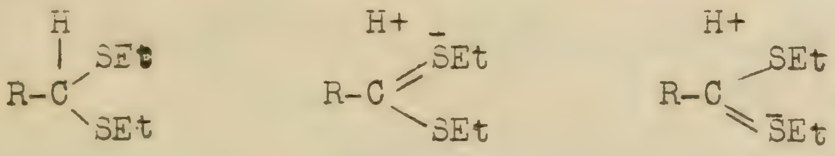
EXPERIMENTS WITH THIOACETALS AND RELATED SUBSTANCES

Eugene Rothstein, The University, Leeds

It has been suggested that the relatively great mobility of α,γ bis-(ethylsulfonyl)propenes as compared to the corresponding α,γ-bis-quaternary ammonium salts is largely due to resonance between the various canonical structures obtained by the expansion of the valency shell of sulfur.

A. Polar Effect of Sulfur in Thioacetals.

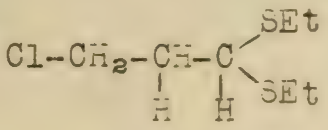
In seeking further experimental evidence as to the possibility of the expansion of the sulfur octet, it was observed that α-benzylsulfonyl-γ-ethylthio-Δ^{α}-propene was tautomeric with its Δ^{β}-isomeride. This suggested that it might be possible to detect a polar effect in sulfides since in these, unlike sulfonyl derivatives, there are no dipoles which can mask any effects due to expansion. A suitable class of substances appeared to be the thioacetals in which there is a possibility of resonance between the following structures:-



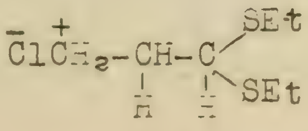
The substances chosen for investigation were the α,α-bis (ethylthio)propenes, and it was in the course of their preparation that the evidence supporting this hypothesis was obtained. Thus, in the following transformation, the Δ^{α}-isomeride (II) was obtained in 77% yield.

$$\underset{\text{I}}{ClCH_2CH_2CH(SEt)_2} \xrightarrow[\text{tert.Butoxide}]{\text{Potassium}} \underset{\text{II}}{CH_3CH{=}C(SEt)_2}$$

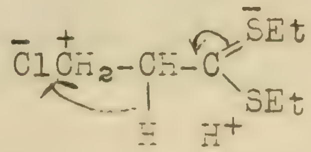
The possible valence structures taking part in the normal state of the chloroacetal (I) are:



i



ii



iii

In the absence of reagents the contributions of structures (ii) and (iii) are apparently small since the substance shows no tendency to lose hydrogen chloride. However, in the presence of the alkoxide ion, the formation of the isomeride (II) is dependent on the possibility of setting up the valency structure (iii).

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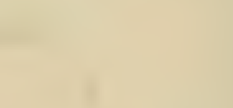

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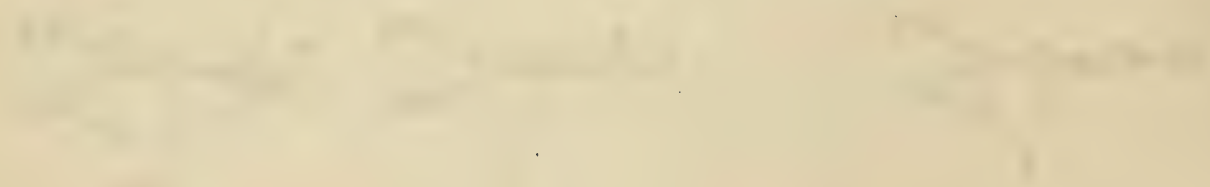

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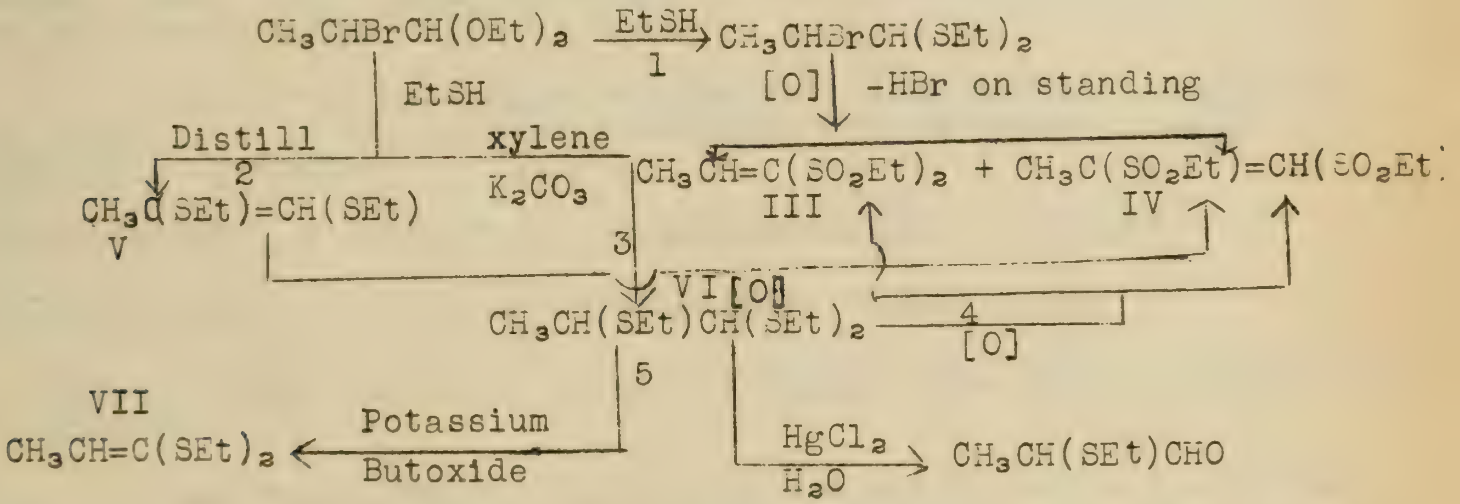
An alternative mechanism which would involve the removal of hydrogen chloride from the γ-chloro-compound, with the subsequent production of the Δ^{β}-isomeride, from which the Δ^{α}-isomeride might be obtained by a protropic change is untenable since both of these compounds are stable in boiling potassium butoxide with no interconversion being apparent.

B. Reaction between α-Bromopropaldehyde Diethylacetal and Ethylthiol.

Unlike γ-chloro-α,α-bis-(ethylthio)propane in which the halogen atom, in the absence of alkali, is relatively stable, it was observed that in the preparation of α,α-bis-(ethylthio)-Δ^{β} propene, $CH_2=CHCH(SEt)_2$, from β,γ-dibromo-α,α-bis-(ethylthio)propane, $CH_2BrCHBrCH(SEt)_2$, that the latter compound tended to lose hydrogen bromide on standing. As a consequence of the hypothesis advance in Part A, it appeared that any β-substituted thioacetal might easily lose the substituent in those cases where the latter might exist as a negative ion. This suggestion is confirmed by the behavior of β-bromo-α,α-bis-(ethylthio)-propane, $CH_3CHBrCH(SEt)_2$ which may be obtained from the corresponding acetal and ethylthiol. The experimental results are diagramed below:

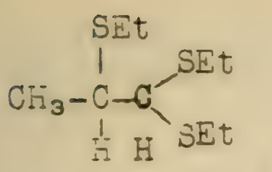


That there is no interchange of ethylthio-groups or their migration does not occur during the course of the above reactions is shown by the synthesis of α,α-bis-(ethylthio)-β-N butylthio propane (VIII) folowed by reactions similar to those of 4 and 5 (above). Oxidation yielded a mixture of the sulfones (III) and (IX) and the action of boiling potassium tert-butoxide resulted in the bis-sulfide (VII)

$CH_3CH(SBu)CH(SEt)_2$ VIII

$CH_3C(SO_2Bu) = CH(SO_2Et)$ IX

For the α,α,β-tris-sulfide there is possibility of resonance between the following valence structures:



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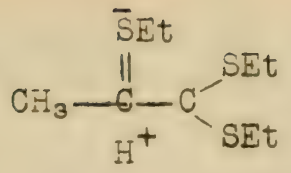
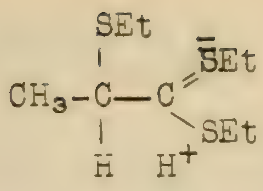


ii



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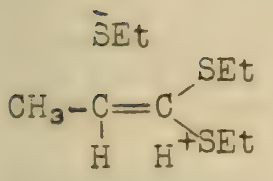

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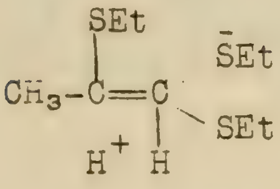


v

The preferential elimination of the β-group as a result of boiling the substance with alkoxide takes place because of the greater contribution of the structure (iii) as compared with that of (ii). Such eliminations cannot be dependent on a mechanism involving the +M effect, which undoubtably would promote the ionization of the halogen atom, since simultaneously it would prevent the release of the α-hydrogen atom.

Rothstein has suggested the following scheme to explain the production of the various substances from β-bromo-α,α-bis-(ethylthio)-propane:

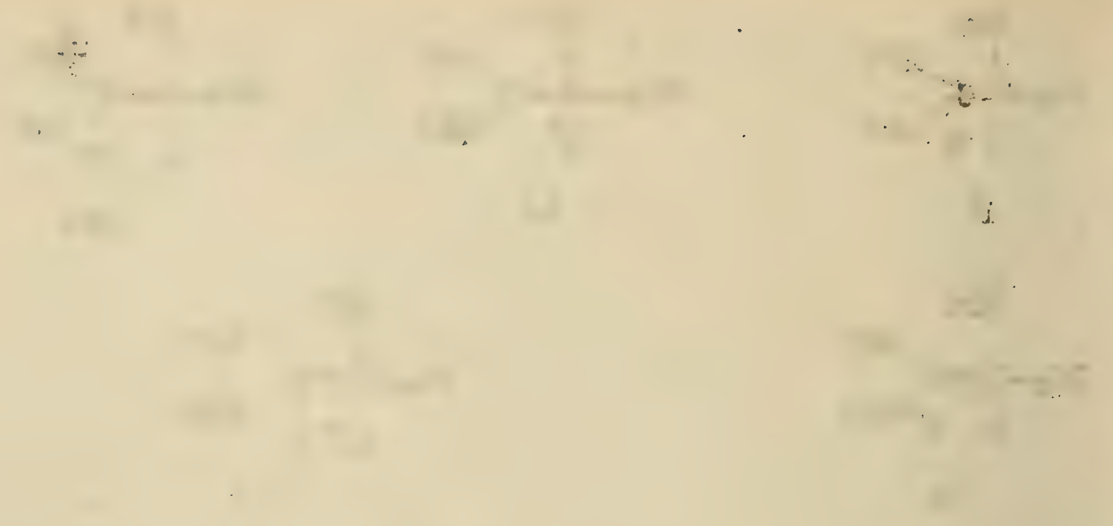
$$CH_3CHBrCH(SEt)_2 + EtSH \rightleftharpoons (VI)CH_3CH(SEt)CH(SEt) + HBr \rightleftharpoons$$

$$CH_3CH(SEt)CHBrSEt + EtSH \rightarrow (V)CH_3C(SEt){=}CH(SEt) + HBr$$

C. Comparison of the Polar Effect of Sulfur with that of Oxygen and Nitrogen.

The reactions of thioacetals noticed in Parts A and B are dependent upon the existence of valence structures which may arise as a result of the expansion of the valency shell of sulfur. Since this phenomenon is not possible in the cases of oxygen and nitrogen, neither the formation of the Δ^{α}-unsaturated compound from the γ-chloro-derivative nor the extremely facile release of the β-halogen atom should be observed in cases analogous to thioacetals.

That in some way a mesomeric effect might be responsible for the formation of the Δ^{α}-propene from γ-chloro-α,α-bis-(ethylthio) propane is eliminated by the observation of Knorr and Roth that dimethyl-γ-chloropropylamine yields the γ-ethoxy-derivative when treated with sodium ethoxide. It might have been expected that the influence of the lone electrons on the sulfur atom would have been exerted by the corresponding electrons on the tertiary nitrogen also. Any possibility that a group with a -I effect might enable this reaction to take place as a result of the potential loosening of the



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α-hydrogen atom is negatived by the observation that trimethyl-γ-chloropropylammonium chloride yields only trimethylallylammonium salts.

A direct comparison between the effects of oxygen and sulfur is shown by the fact that treatment of the γ-chloropropaldehyde diethylacetal with potassium butoxide resulted in the formation of acraldehyde diethylacetal, $CH_2=CH-CH(OEt)_2$, without the appearance of any methylketene diethylacetal. The latter was shown not to be an intermediate as indicated by its stability to the above reagent.

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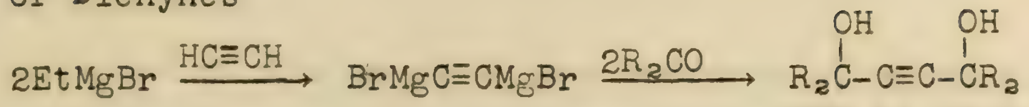
Reported by J. M. Wilkinson, Jr.
February 19, 1941

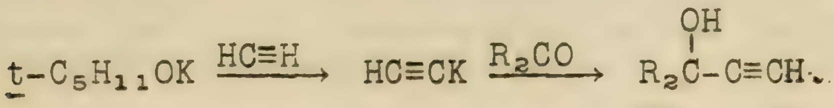
CYCLIZATION OF DIENYNES

I Synthesis of Dienynes

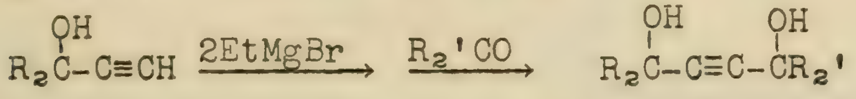
A. 

$$2EtMgBr \xrightarrow{HC\equiv CH} BrMgC\equiv CMgBr \xrightarrow{2R_2CO} R_2\overset{OH}{\overset{|}{C}}-C\equiv C-\overset{OH}{\overset{|}{C}}R_2$$

60% based on R_2CO

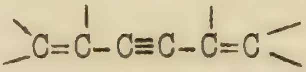
B. 

$$\underline{t}-C_5H_{11}OK \xrightarrow{HC\equiv H} HC\equiv CK \xrightarrow{R_2CO} R_2\overset{OH}{\overset{|}{C}}-C\equiv CH. \quad 80\%$$



$$R_2\overset{OH}{\overset{|}{C}}-C\equiv CH \xrightarrow{2EtMgBr} \xrightarrow{R_2'CO} R_2\overset{OH}{\overset{|}{C}}-C\equiv C-\overset{OH}{\overset{|}{C}}R_2' \quad 40\% \text{ overall}$$

acetylenic glycols $\xrightarrow[K_2S_2O_7 \text{ or } 40\% \; H_2SO_4]{85-95\% \text{ yield}}$



$$>C=\overset{|}{C}-C\equiv C-\overset{|}{C}=C<$$

dienynes

II Properties of Dienynes

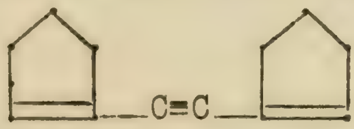
A. Ozonization has confirmed the rule of Thoms and Ambrus that unsymmetrical tertiary alcohols dehydrate in the longer chain.

B. $HgSO_4$ converts dienynes to tetrahydroketofurans.

C. Maleic anhydride addition to dienynes and cumulene formation from dienynes have been presented before this seminar previously.

D. Dienynes can be cyclized by sulfuric or formic acid to alicyclic unsaturated ketones under the following conditions:

1. If the dienyne is less substituted than RCH=CR-C≡C-CR=CHR, and in the special case

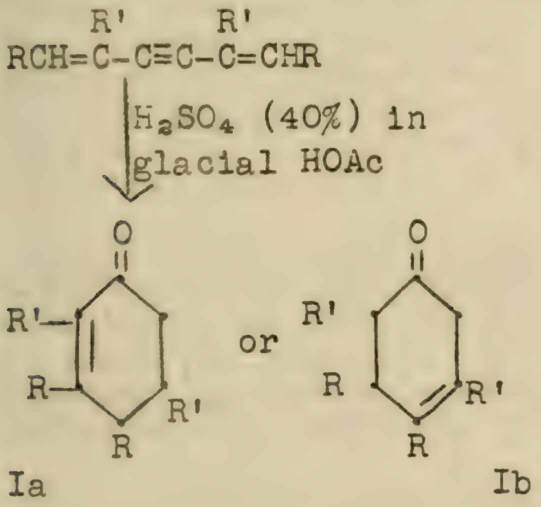


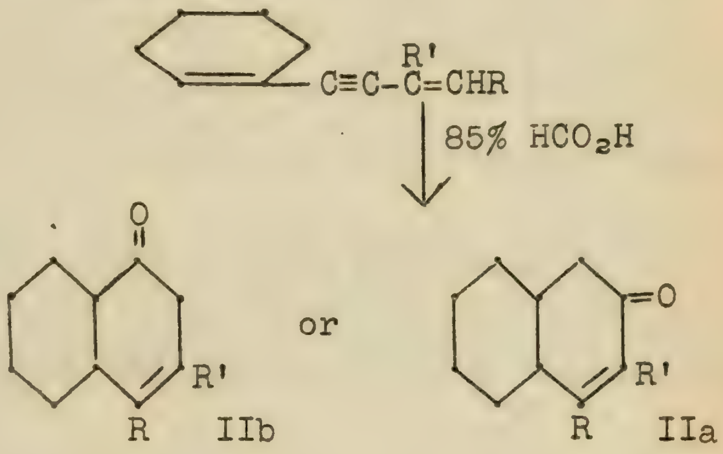
only polymerization occurs.

2. At least one of the carbons at the end of the dienyne system must carry a hydrogen.
3. The double bonds may not be parts of aromatic systems nor more than one of them conjugated with an aromatic ring.
4. One or both of the double bonds may be part of an alicyclic ring, for example cyclohexene or octalin.

III Cyclization Products from Dienynes Containing Not More than One Alicyclic Ring.

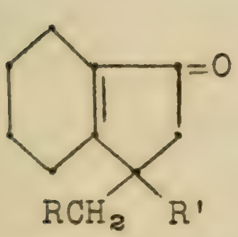
C-H analysis indicates that one molecule of water adds to the dienyne on treatment with sulfuric or formic acid at room or ice temperature for ten hours. Derivatives show the oxygen to be ketonic. Ozonization of the unsaturated ketone indicates but does not differentiate the following structures:



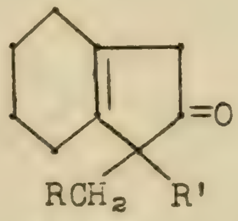


In both cases 50-60% yields of 2° fractions (reduced pressure) of the liquid ketones are obtained and although two racemic modifications are possible in each case, single derivatives are obtained.

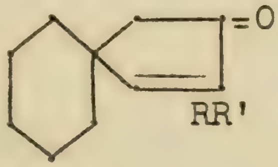
There is some evidence that II either contains some isomeric spirane III which can be isomerized to a blue azulene IV or can itself be isomerized to an azulene. The Clemmensen reduction product of II analyzes for an octalin and on repeated dehydrogenation over Pd-charcoal at 300° Mozingo isolated, not a naphthalene, but a deep blue hydrocarbon in 19% yield. C-H analysis, spot test, and absorption spectra indicated that this was a hydroazulene.



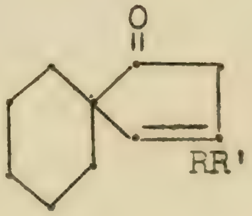
IIIa



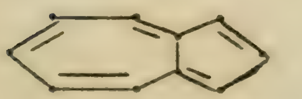
IIIb



IIIc



IIId



IV

Recently Brooks seems to have obtained an azulene by dehydrogenation of a known spirane.

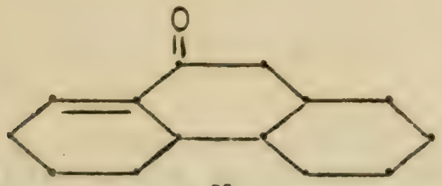
IV Products from Dienynes Containing More than One Alicyclic Ring

At least two isomers are usually obtained in cyclization which is carried out at 0° and with slightly better yields by formic than sulfuric acid in some cases. Both isomers analyze for the unsaturated alicyclic ketone and usually one crystallizes and gives ketone derivatives. The isomeric liquid, however, gives ketone derivatives only after boiling with concentrated HBr, or not at all. If a ketone derivative is obtained by this method, it is isomeric with that from the solid ketone after reduction of the double bond.

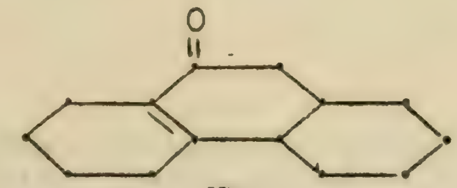
$\Delta^{1,1'}$ Considerable work has been done on the product from di--cyclohexenylacetylene. Two solid ketones are obtained in this case, 4% of a 94° ketone and 60% of a 39° ketone. Neither of these is identical with the Δ^{10}-dodecahydro-9-phenanthrone (89°) obtained by Rapson and Robinson from the condensation of sodiocyclohexanone and acetylcyclohexene.

From the difficulty of dehydrogenation over Se, the fact that dienynes from trans-decalones cyclize in much better yield than those from cis-decalones, and slight further evidence, it has been assumed that the dienyne ring closure takes place trans.

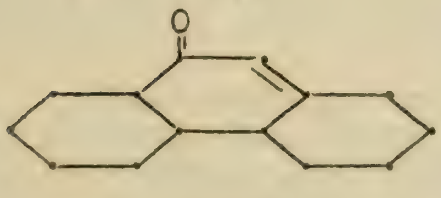
Assuming the 94° and 39° ketones to be isomeric, trans, conjugated dodecahydrophenanthrones (evidence for conjugation presented later), Linstead has used these in his study of the stereoisomerism of the perhydrophenanthrones and perhydrodiphenic acids. The possibilities are:



Va



Vb



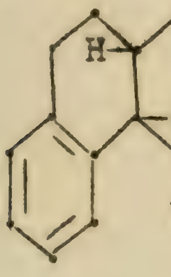
Vc

Hydrogenation (Pd-charcoal) of the 94° and 39° ketones gave the same two isomeric perhydro-9-phenanthrones from each, mainly a 51° saturated ketone, the second perhydrophenanthrone being isolated only as the oxime, m.p. 186°. The cyclization products must, therefore, be Va and Vb. (Had it been indicated that one was Vc, it would have been necessary to assume Rapson and Robinson's ketone to be the cis-racemic modification.)

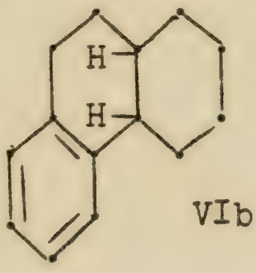
Reduction of Rapson and Robinson's ketone gave a third perhydro-9-phenanthrone melting at 49°. Linstead and Marvel obtained independently the fourth and final racemic perhydrophenanthrone, the latters synthesis utilizing the hydrogenation of 9-phenanthrol.

By the oxidation of the perhydrophenanthrones and hydrogenation of methyldiphenate, Linstead obtained four new perhydrodiphenic acids and one of the two reported by Vocke. All but that from the cyclization products and that one of Vocke's acids which may or may not be identical with this gave perhydrofluorenones by the Blanc method. All gave cyclic anhydrides. Exceptions to Blanc's rule have been previously found among steroids.

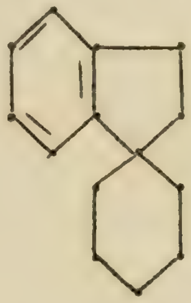
The unsaturated hydrocarbon produced by Clemmensen reduction of the main (39°) cyclization product gives on Se dehydrogenation a product analyzing for and having the properties of the following mixture shown to be inseparable by fractionation by Cook, Hewett, and Robinson. The precourser of VII would yield a diphenic acid which as a 1,3-dicarboxylic acid should not give a ketone. Furthermore, Bogert has shown that spiranes may dehydrogenate to aromatic hydrocarbons; therefore, this cannot be used to disprove the existence of a spirane in a particular case. (The cyclization products dehydrogenate with Pt-carbon in a better yield, 50-70% in some cases, than would be expected from spiranes.)



VIa



VIb



VII

The question of whether or not the cyclization products are or contain spiranes is being investigated here both by the synthesis of spiranes and the attempted synthesis of 9-perhydrophenanthrene by other methods.

Clemmensen reduction of unconjugated unsaturated ketones yields olefins, but of conjugated unsaturated ketones normally yields bimolecular reduction products or saturated alcohols. In spite of the Clemmensen reduction of the unsaturated cyclization product ketones to olefins, the 39° ketone has been proved to be conjugated.

Pearson brominated the 51° perhydrophenanthrene and dehydrobrominated with pyridine to obtain a main product identical with the 39° ketone, proving this to be conjugated. Linstead had previously indicated this by absorption spectrum measurements and because of the slowness (although unusually variable in this series) of iodine monochloride to the cyclization products.

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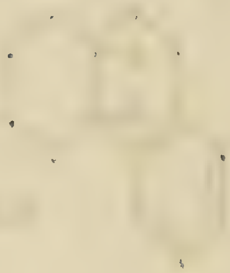

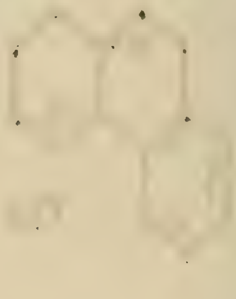

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Reported by G. D. Jones
February 26, 1941

FLUORINATION OF ALIPHATIC ORGANIC COMPOUNDS

L. A. Bieglow, Duke University; A. L. Henne, Ohio State University

During recent years aliphatic fluorine compounds have attained considerable importance. The chlorofluore derivatives have been developed as so-called safety refrigerants under the collective name of "Freon." Further, since fluorine is the most reactive, as well as the most electro-negative, of all the elements, its properties, when substituted in organic compounds, are significant.

Early investigators reported that fluorination of organic compounds with elementary fluorine proceeds with explosive violence, and until several years ago this method of introducing fluorine was thought to be of no value in synthetic work. At that time Bigelow at Duke began a careful study of the subject and has since effected several changes in the methods employed. In particular, he has made use of copper as the catalyst in the operation. The sample is placed in a horizontal tube, between two suitably heated rolls of copper gauze. The fluorine, which is generated by electrolysis of potassium bifluoride and must be pure and anhydrous, is diluted with nitrogen and introduced at the center of one of these rolls. Under appropriate conditions, a perfectly quiet, continuous reaction occurs. The products are condensed and then purified and rectified in a Podbielniak still. Using this technioue Bigelow has studied the vapor phase fluorination of methane, ethane, ethyl chloride and hexachlorethane. By proper dilution of fluorine with nitrogen yields of better than 90% of recoverable products have been obtained.

Fluorination of ethane has yielded products which would be expected on the basis of a free radical mechanism. Similar treatment of methane yields CH_3F, CH_2F_2, CHF_3, CF_4, together with hexafluoroethane C_2F_6 and octafluoropropane C_3F_8. All of these results are in accord with the current free radical chain mechanism now used by Haas and others to explain vapor phase chlorination and which may be illustrated as follows:

$$F_2 \rightarrow 2F\cdot \qquad (1)$$

$$CH_4 + F\cdot \rightarrow CH_3\cdot + HF \qquad (2)$$

$$CH_3\cdot + F_2 \rightarrow CH_3F + F\cdot \qquad (3)$$

The chain continues until CF_4 is finally formed. Here (1) presumably must be either thermal or catalytic. The formation of C_2F_6 is easily explained by:

$$CHF_3 + F\cdot \rightarrow CF_3\cdot + HF \qquad (4)$$

$$2CF_3\cdot \rightarrow C_2F_6 \qquad (5)$$

and that of C_3F_8 according to the equations:

$$CH_2F_2 + F\cdot \rightarrow CHF_2\cdot + HF \qquad (6)$$

$$CHF_2\cdot + CF_3\cdot \rightarrow CF_3CHF_2 \qquad (7)$$

$$CF_3CHF_2 + F\cdot \rightarrow CF_3CF_2\cdot + HF \qquad (8)$$

$$CF_3CF_2\cdot + CF_3\cdot \rightarrow C_3F_8 \qquad (9)$$

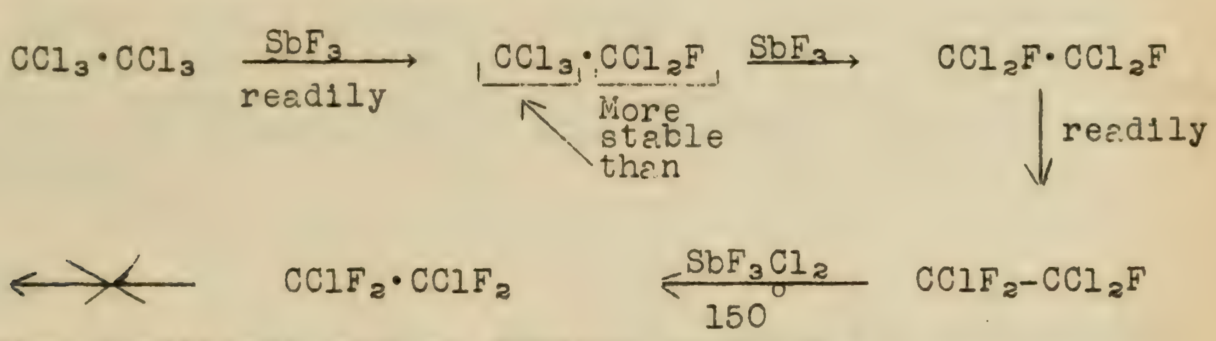
Equation (7) is supported by the fact that Bigelow obtained definite evidence, although not conclusive proof, of the presence of some CF_3CHF_2 in the product. Still further support for the free radical interpretation can be found in a recent paper by Miller at Cornell who has presented considerable evidence to show that direct fluorinations proceed by a non-ionic mechanism. On the whole, it appears that direct fluorination is more similar to chlorination than had been supposed earlier.

The classical method of synthesis of aliphatic fluorine compounds is that developed by Swarts in 1896 which consists in heating together a mixture of a polychloroethane and antimony trifluoride in the presence of about 10% antimony pentachloride. This procedure has been somewhat modified by Henne at Ohio State. The latter works with steel equipment, performs the fluorination under pressure and removes the desired fluorinated derivatives from the reaction field as soon as formed.

Henne has used a variety of fluorinating agents. Antimony trifluoride and SbF_3Cl_2 were found preferable for fluorinating compounds rich in halogen atoms, such as CCl_4, $CHCl_3$, and $CHBr_2CHBr_2$; they are convenient reagents to get $-CX_2F$, $-CXF_2$, $-CHXF$, and $-CHF_2$ groups, and, in rare cases, a $-CF_3$ group. In this earlier work silver fluoride and mercurous fluoride were used on bromides or iodides containing not over one halogen atom. However, for compounds with sluggish halogen atoms mercuric fluoride has been found to be by far the most powerful and convenient fluorinating agent. It is most readily employed by passing hydrogen fluoride through a well-stirred mixture of mercuric oxide and the substance to be fluorinated. Reaction between the oxide and the acid occurs instantly and so also does the one between the mercuric fluoride so generated and the organic material.

The first studies were made on the following halogenated derivatives of ethane: C_2Cl_6, $CHCl_2CCl_3$, CH_2ClCCl_3, and $CHCl_2CHCl_2$. The first listed compound is fluorinated symmetrically to the $CClF_2CClF_2$ stage; the second is converted asymmetrically to the $CHCl_2CClF_2$ stage, very little to CHF_2CClF_2. A second hydrogen atom on the same carbon atom is found to influence the course of fluorination even more markedly. A mono- and a difluoride, CH_2ClCCl_2F and $CHCl_2CClF_2$, are obtained. The $-CH_2Cl$ group remains perfectly inert toward further fluorination even under most severe conditions. When the two hydrogen atoms are on different carbon atoms the products are $CHCl_2CHF_2$ and $CHCl_2CClF_2$; with mercuric

fluoride CHF_2CHF_2 is obtained by asymmetrical substitution; with SbF_3Cl_2 as reagent and under more severe conditions the products first formed undergo rearrangement or give CH_2ClCF_3. Under all of these conditions there is a tendency to lose hydrogen halides, to rearrange and to resist fluorination with antimony trifluoride. Investigation was continued with fluorinated halo derivatives having three or four hydrogen atoms. It was found that when the halogen atoms are all located on the same carbon atom, fluorination proceeds rapidly to completion, without simultaneous chlorination or loss of hydrogen halides. In marked opposition, derivatives having both a hydrogen and a halogen on each of their carbon atoms are quite resistant to fluorination with antimony trifluoride, and when they are affected they undergo considerable chlorination and decomposition. Moreover, in all cases except the hexachloroethane derivatives, these fluorinated compounds exhibit a marked difference in their stability in favor of the asymmetrical compounds. Some idea of the stabilizing effect of the fluorine atom is shown in the fluorination of hexachlorethane with antimony trifluoride:



Most severe conditions gave no further reaction.

Methane derivatives have also been studied. Difluorides could be obtained by treatment of methylene chloride and chloroform with antimony trifluoride; however, fluoroflor could be obtained only by the action of mercuric fluoride on $CHClF_2$.

Summing up Henne's observations on stability of products formed during fluorination:

1. The presence of a lone fluorine atom in an aliphatic molecule produces an unstable compound which shows a great tendency to liberate hydrogen fluoride.

2. In contradistinction, compounds having a halogen atom on the carbon bearing the fluorine are more stable.

3. The presence of two fluorine atoms on the same carbon is attended by:
   a. very great increase of strength of the C-F bonds;
   b. strengthening of the linking of any third halogen atom that may be present on the same carbon atom;
   c. great increase of the stability of any halogen atoms present on adjacent carbon atoms.

In the desire to study the influence of an isolated difluoro group in a molecule, Henne synthesized 2,2,-difluoropropane from the corresponding dichloro compound. The reaction went readily at room temperature with antimony trifluoride, the ease and completion of the fluorination being due to the fact that all the halogen atoms were gathered on a single carbon atom, in a group isolated within the molecule. Experiments were made on the further fluorination and the chlorination of this molecule; the results confirmed the opinion expressed above regarding the stabilizing effect of a =CF- group. The physiological inertness of a compound stabilized in this manner is well illustrated by the fact that animals can be kept in an atomsphere of 20% oxygen and 80% $CH_3CF_2CH_3$ for hours without effect. Henne accounts in part for the difference in stability between these difluorides and the monofluorides on the basis of bond lengths; the distance between carbon and fluorine in the polyfluorides is only 1.36 A^o as against 1.42 A^o for monofluorides as shown by X-ray diffraction studies.

Further investigations on propane indicate (from the practical standpoint) that high molecular polyfluorides should be synthesized by condensation of smaller highly fluorinated molecules, rather than by the fluorination of high molecular compounds obtained by condensation.

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Reported by L. J. Armstrong
February 26, 1941

STRUCTURE OF ORGANIC MOLECULES FROM MONOMOLECULAR FILMS

N. K. Adam, University College, Southampton
I. Langmuir, General Electric Company

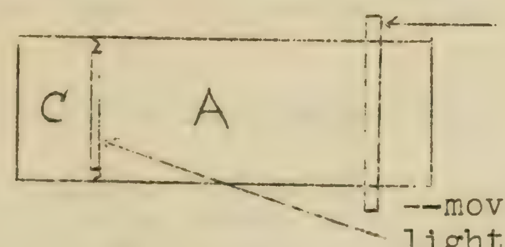
If a small quantity of a practically insoluble and non-volatile substance is placed on a clean water surface, it either remains as a compact drop or it may spread out over the surface to form a film one molecule deep. Spreading occurs when the adhesional forces are greater than the cohesional forces.

Monolayers may exist in different forms, which correspond, in two dimensions, to the three principal states of matter in three dimensions -- solid, liquid, and gaseous. The stability of a monolayer is determined by the strength of the anchorage of the molecules to the water surface; its state is determined by lateral cohesion.

Experimental Methods:

The surface pressure of a film is measured by forming a layer of the compound (A) on pure water in a trough coated with paraffin wax (Fig. I). The force (expressed in dynes per cm.) represents the pressure exerted on the float D by the compound against the clean water surface C.

Figure I



--movable barrier

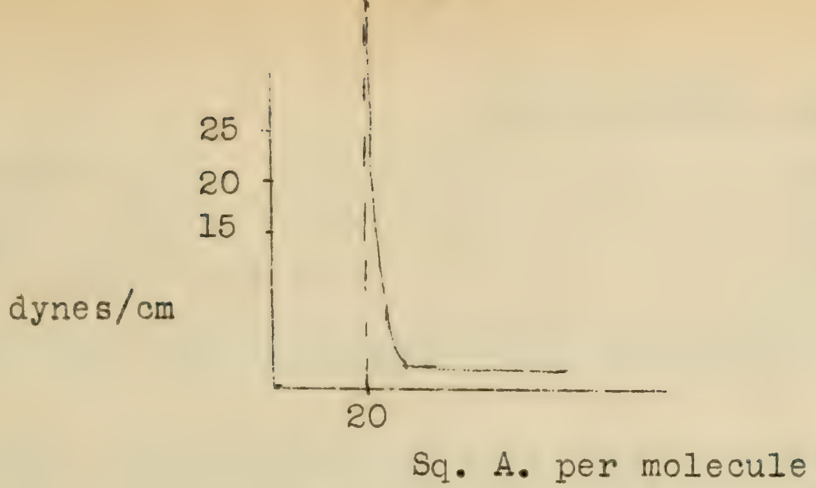
light float D connected to a torsion balance

For measuring surface potential, a cell is used which consists of a standard electrode connected with the water by a salt bridge. The other electrode is a metal plate suspended as close as possible above the film A. A particle of a polonium compound is placed on the electrode in order to ionize the intervening air. The potential is measured by means of a potentiometer.

Types of Films:

In condensed films the molecules adhere to each other laterally and very strongly. The pressure-area curve shows a sudden development of pressure as the area is reduced to that at which the molecules are closely packed.

Figure II



The saturated, straight-chain fatty acids containing from 14 to 34 carbon atoms all give the same curve. Since the length of the chain makes no difference, the molecules must either be vertical, with the hydrophilic carboxyl groups down in the water, or the chains must be steeply oriented, all at the same angle. The cross-section of a single molecule, measured by surface films, is 20.5 sq.A, compared to 18.4 sq.A. from X-ray data on the crystal.

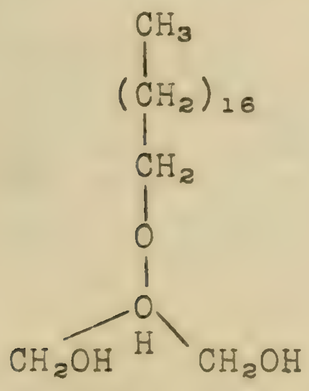
An ideal gaseous film would consist of molecules of negligible size, insoluble in water, and without any lateral cohesion, although with sufficient adhesion for water to prevent their flying off as a vapor. By the kinetic theory such an ideal gaseous film would have a surface pressure F where

$$FA = kT$$

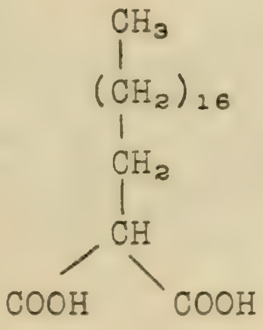
In the most common type of gaseous films, the molecules lie flat on the surface.

Application to Structure Determination:

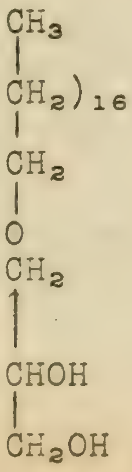
Batyl, chimyl, and selachyl alcohols were isolated from shark liver oil and were shown to be monoglyceryl ethers of octadecyl, cetyl, and oleyl alcohols respectively. It was difficult to show whether they were α- or β-glyceryl ethers. Batyl and chimyl alcohols formed good condensed films. Knight obtained the following results and assigned structure III to batyl alcohol.



I

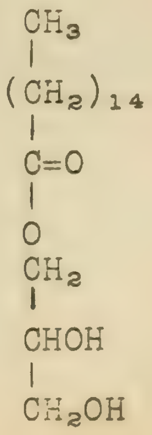


II



$CH_3(CH_2)_{16}CH_2OCH_2CHOHCH_2OH$

III



$CH_3(CH_2)_{14}C{=}O\,OCH_2CHOHCH_2OH$

IV

Substance	Cross section -sq.A. per molecule
α-monoglycerides IV	26.3
batyl alcohol	26.0
chimyl alcohol	28.6
monooctadecylmalonic acid II	36.0

Heilbron confirmed this conclusion later from purely chemical evidence.

In the investigation of more complicated molecules scale models were used. Adam had found that the horizontal cross-section of the rectangular parallelpiped just enclosing these models is usually a close approximation to the area actually occupied in the film, and is practically never less than this.

The old sterol formula required in any direction at least 54 sq. A. The new formula, when the hydroxyl is at C-3, requires 35-40 sq. A. depending on the configuration.

Experimental Results:

	Cross section sq. A per molecule
ergosterol	38
cholestanol	39
cholesterol	41
epi-cholestanol	41
coprostanol	42
epi-coprostanol	44

Although surface film data were available on sterols as early as 1923, no one had sufficient confidence in their interpretation, prior to 1932, to dispute the old formula seriously. The actual revision was inspired chiefly by Bernal's X-ray measurements and the reinterpretation of chemical evidence.

Drake and Wolfe have recently used monomolecular film measurements in the study of cerin and friedelin.

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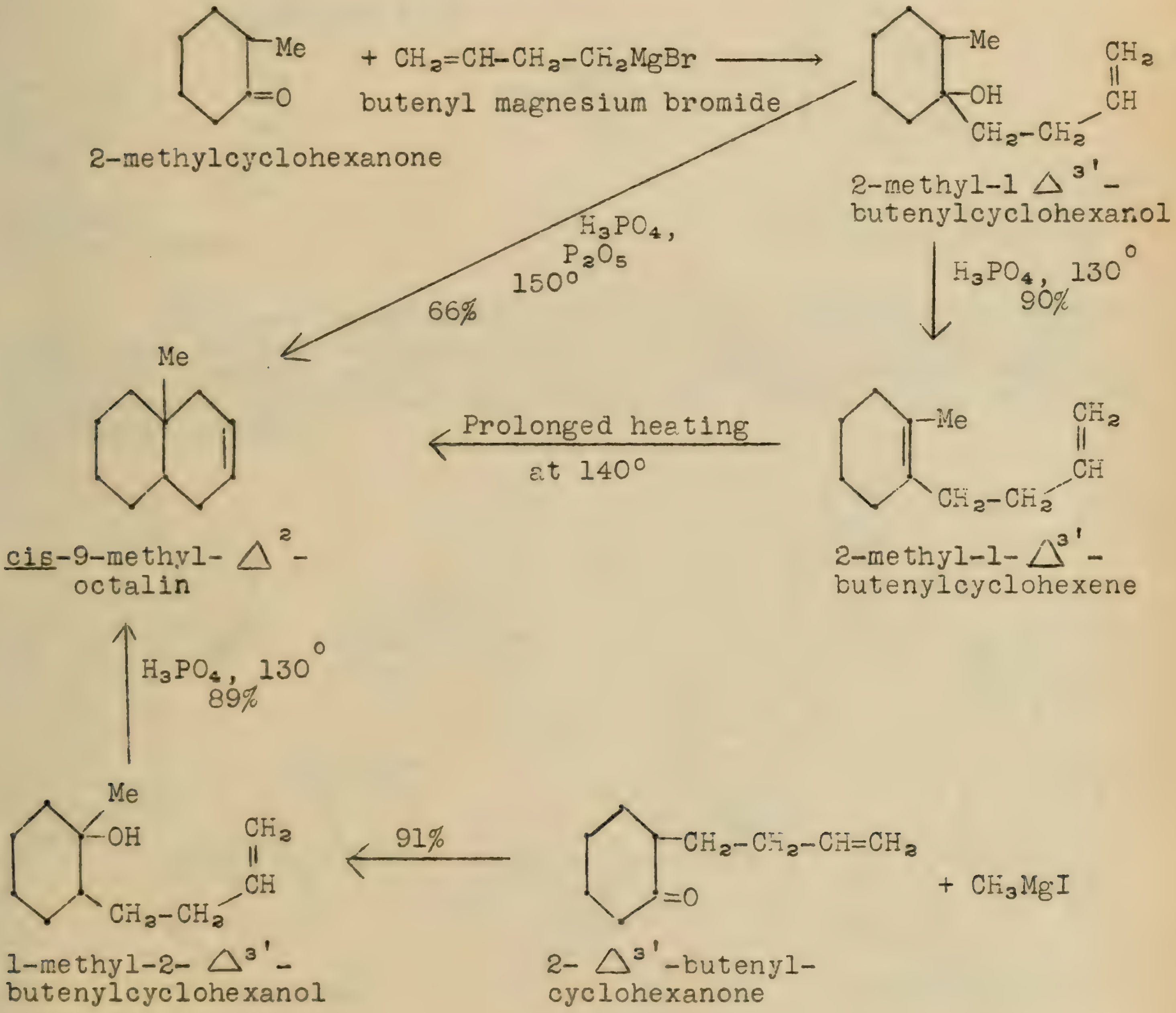
Reported by R. F. Phillips
March 5, 1941

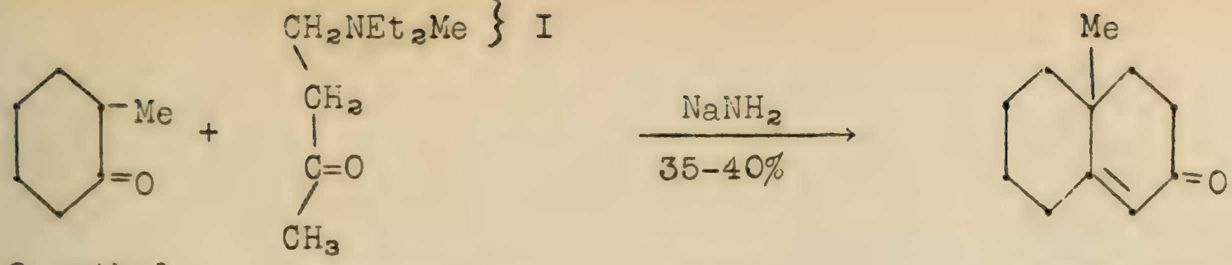
INTRODUCTION OF THE ANGULAR METHYL GROUP

Due to the importance of sterol syntheses, several methods have been devised for the introduction of the angular methyl group into cyclic compounds.

Linstead studied the dehydration of 2-methyl-1-$\Delta^{3'}$-butenylcyclohexanol:



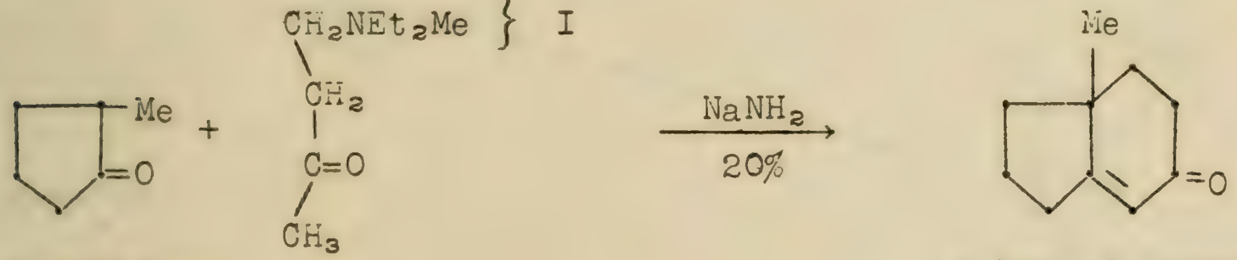
One of Robinson's methods depends on the condensation of simple ketone derivatives with a methyl-substituted cyclic ketone. Quaternary ammonium salts, being in this case the methiodides of bases prepared by the Mannich reaction, were condensed with the sodium derivatives of ketones:



2-methyl-cyclohexanone

4-diethylaminobutane-2-one methiodide

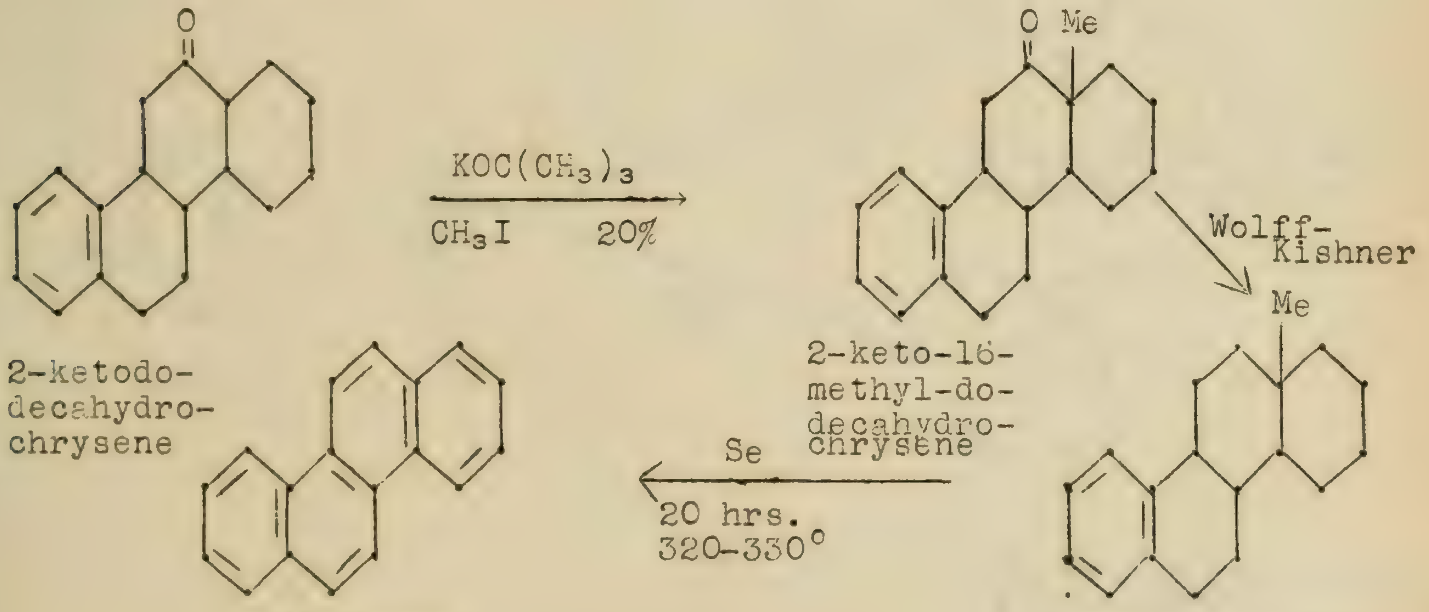
2-keto-10-methyl-$\Delta^{1,9}$-octalin



2-methyl-cyclopentanone

5-keto-8-methyl-$\Delta^{4,9}$-tetrahydrohydrindene

Robinson contributed another means of preparation when he found that the keto-methylene group in a compound such as 2-keto-dodecahydrochrysene was feebly reactive toward cationoid reagents. The procedure was to treat the ketone with potassium-tert.-butoxide and methyl iodide:



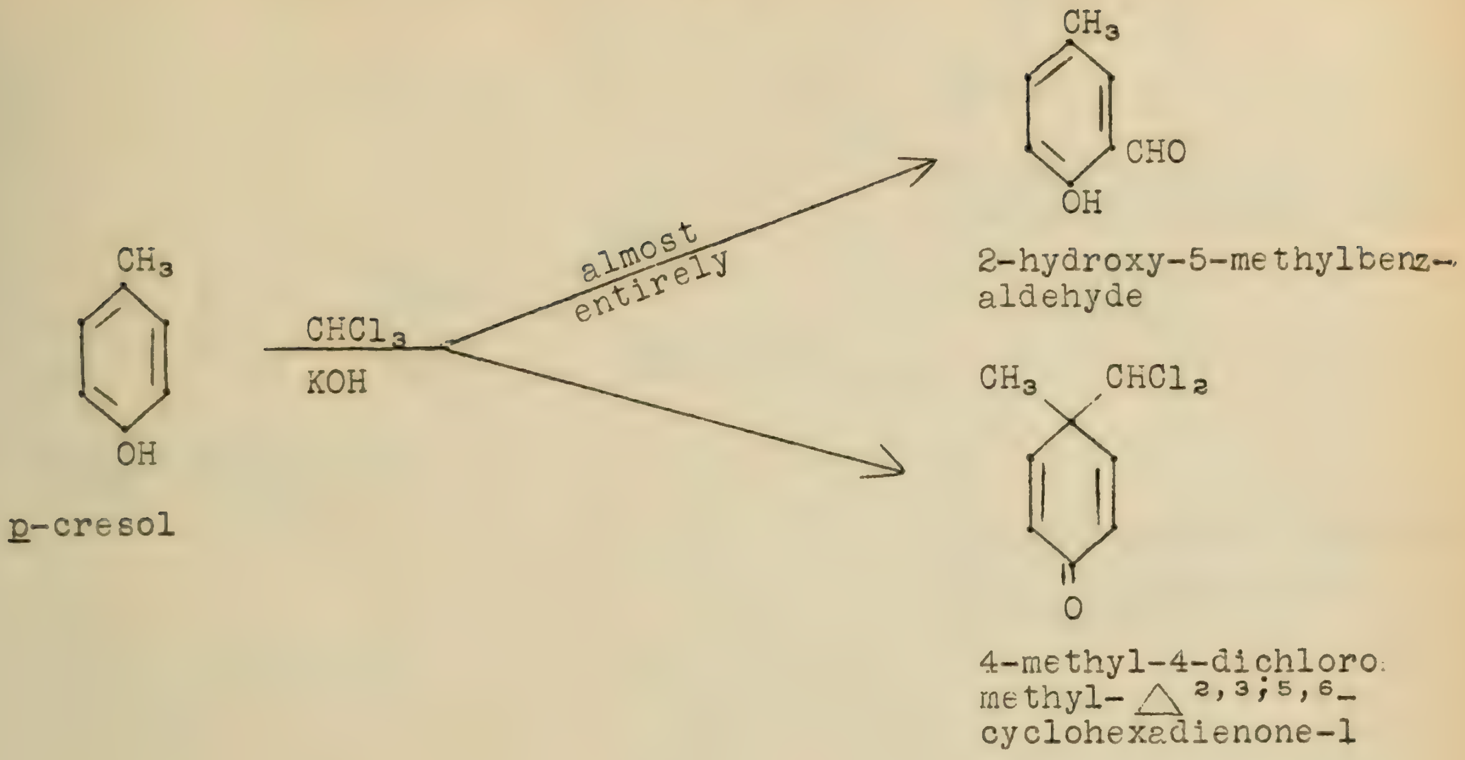
2-ketododecahydrochrysene

2-keto-16-methyl-dodecahydrochrysene

chrysene

16-methyl-dodecahydrochrysene

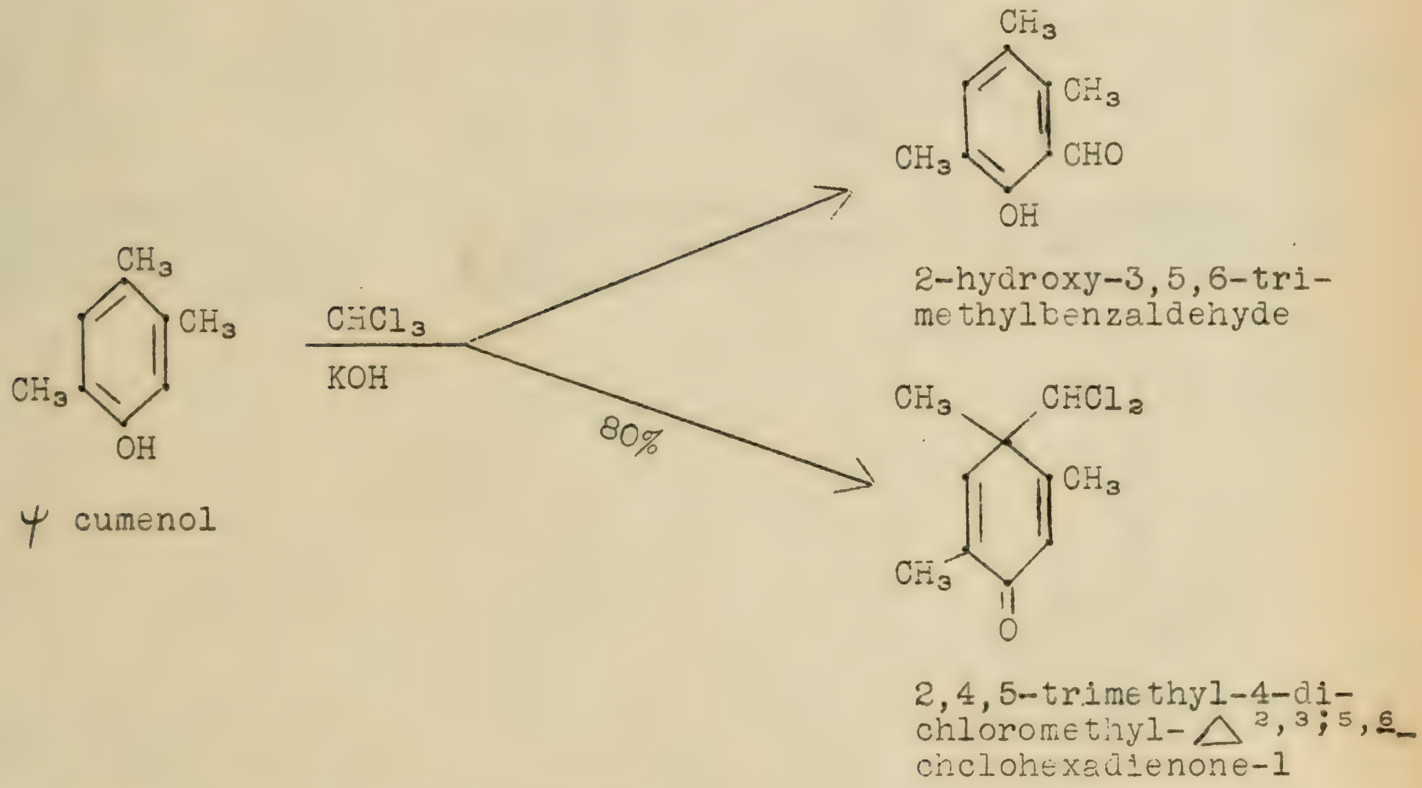
Woodward has developed a method for the direct introduction of the angular methyl group, basing his work on von Auwers' investigation of the Reimer-Tiemann reaction on o- and p-alkyl substituted phenols. von Auwers found that the phenols were converted only in part into the expected aldehydes, the remainder being used in the formation of cyclohexadienones, the ratio of the normal to the abnormal product varying with the structure of the phenol.



p-cresol

2-hydroxy-5-methylbenzaldehyde

4-methyl-4-dichloromethyl-$\triangle^{2,3;5,6}$-cyclohexadienone-1

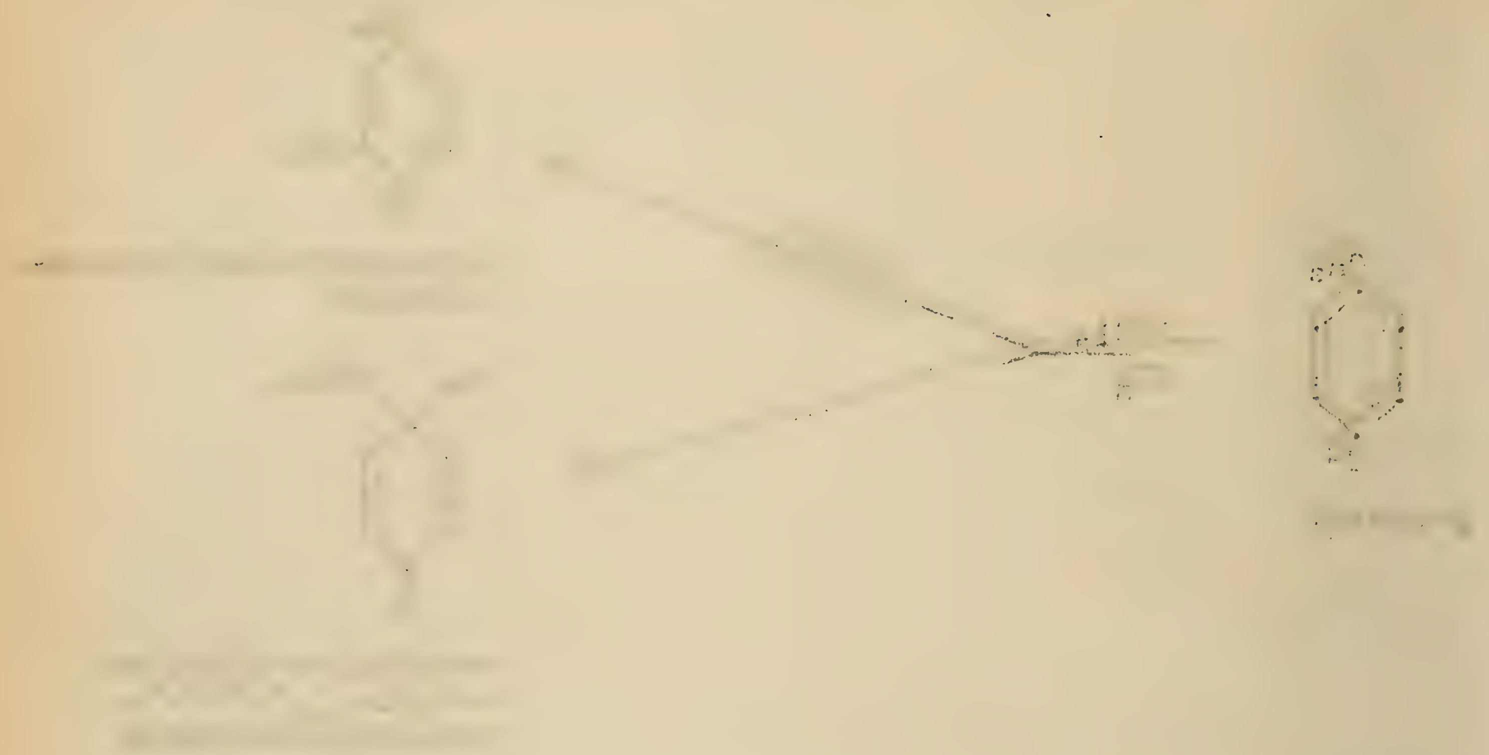


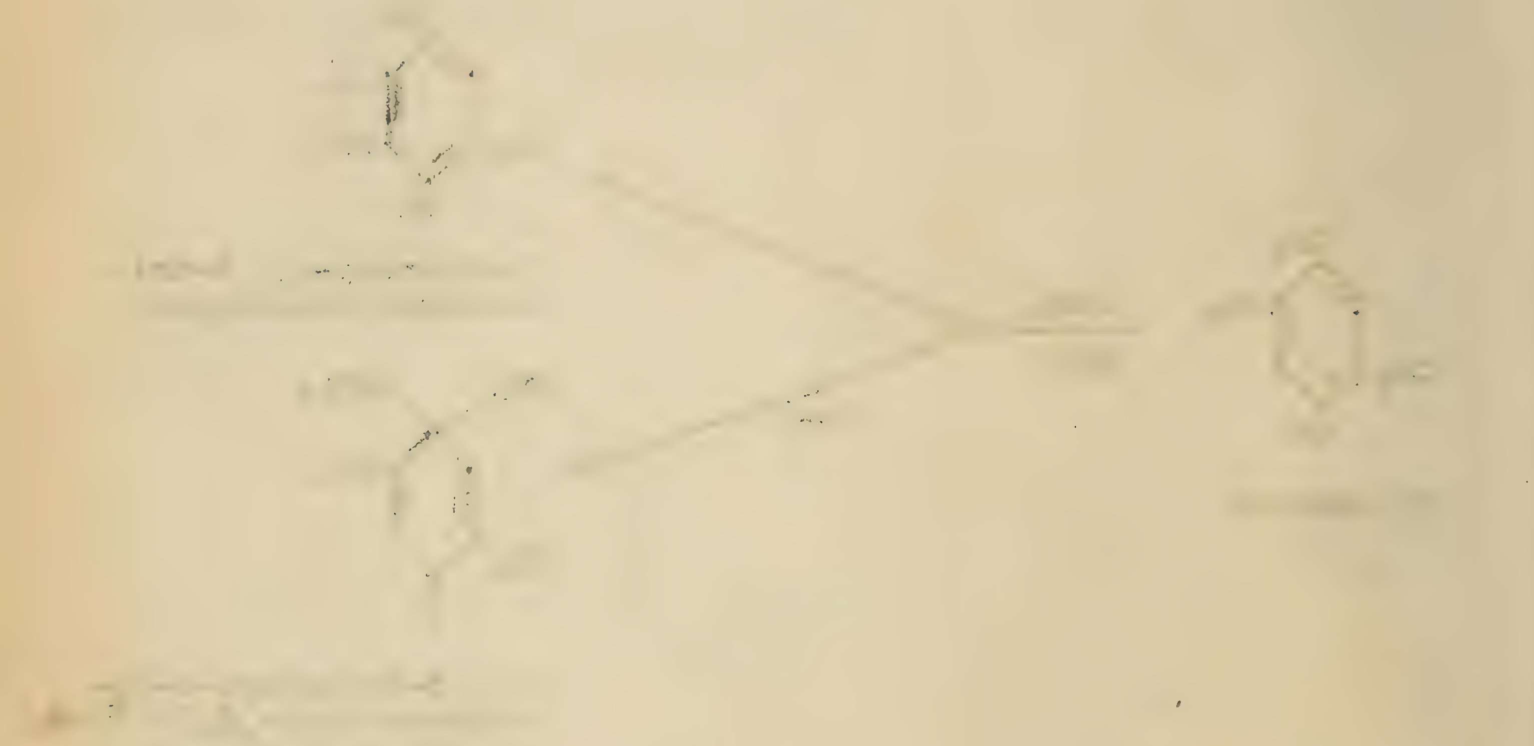
ψ cumenol

2-hydroxy-3,5,6-trimethylbenzaldehyde

2,4,5-trimethyl-4-dichloromethyl-$\triangle^{2,3;5,6}$-chclohexadienone-1

Woodward then studied this reaction on 6-hydroxy-1,2,3,4-tetrahydronaphthalene:





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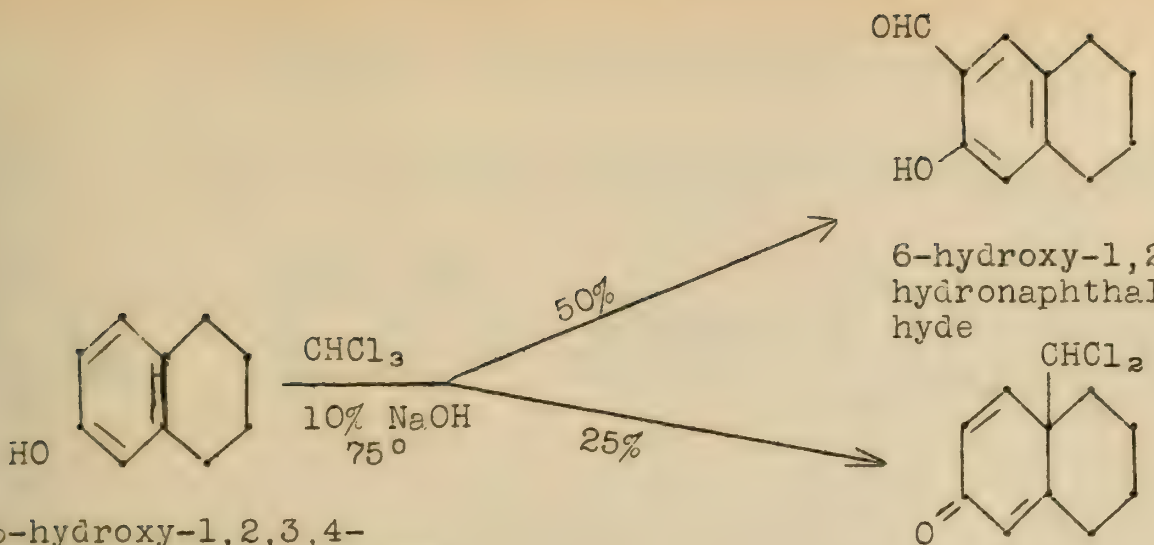
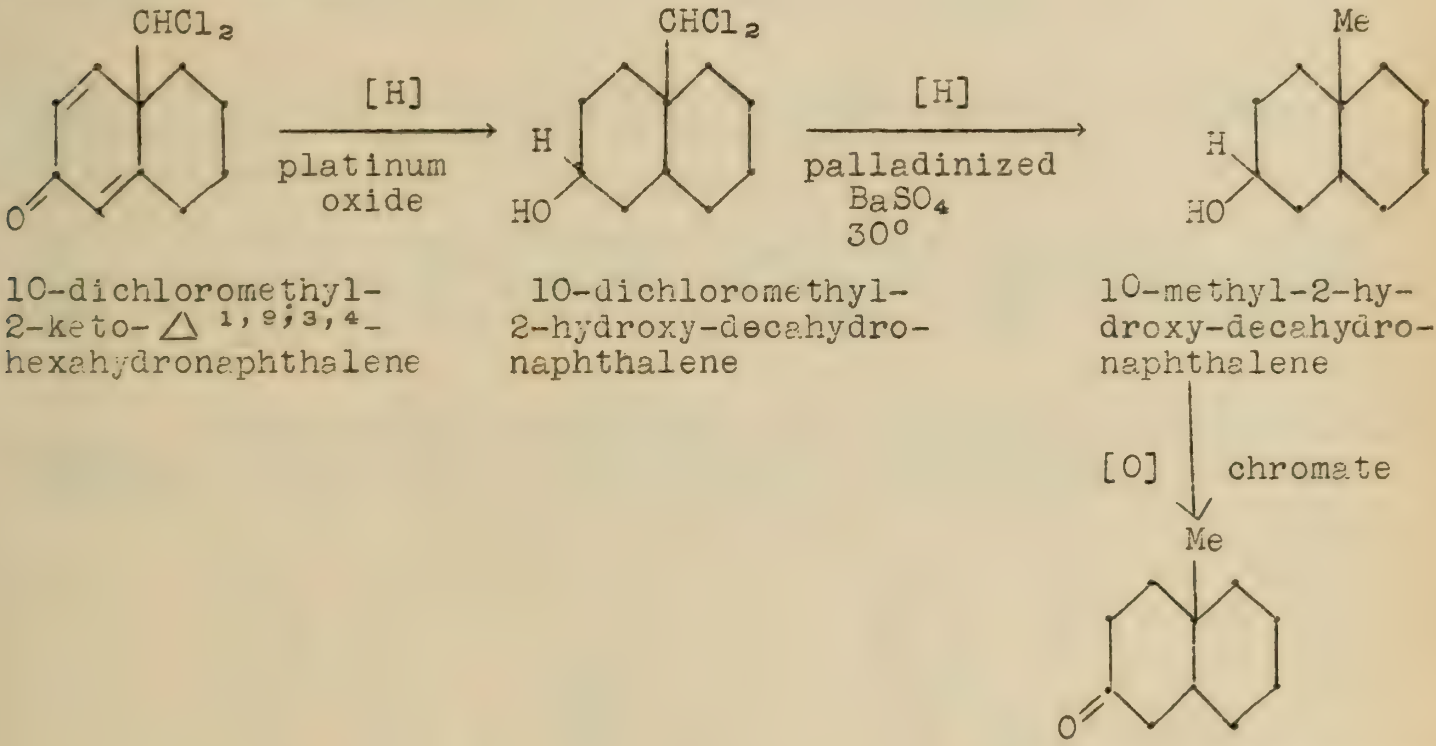


6-hydroxy-1,2,3,4-tetrahydronaphthalene

6-hydroxy-1,2,3,4-tetrahydronaphthalene-7-aldehyde

10-dichloromethyl-2-keto-$\Delta^{1,9;3,4}$-hexahydronaphthalene

Proof of structure:



10-dichloromethyl-2-keto-$\Delta^{1,9;3,4}$-hexahydronaphthalene

10-dichloromethyl-2-hydroxy-decahydronaphthalene

10-methyl-2-hydroxy-decahydronaphthalene

10-methyl-decalone-2

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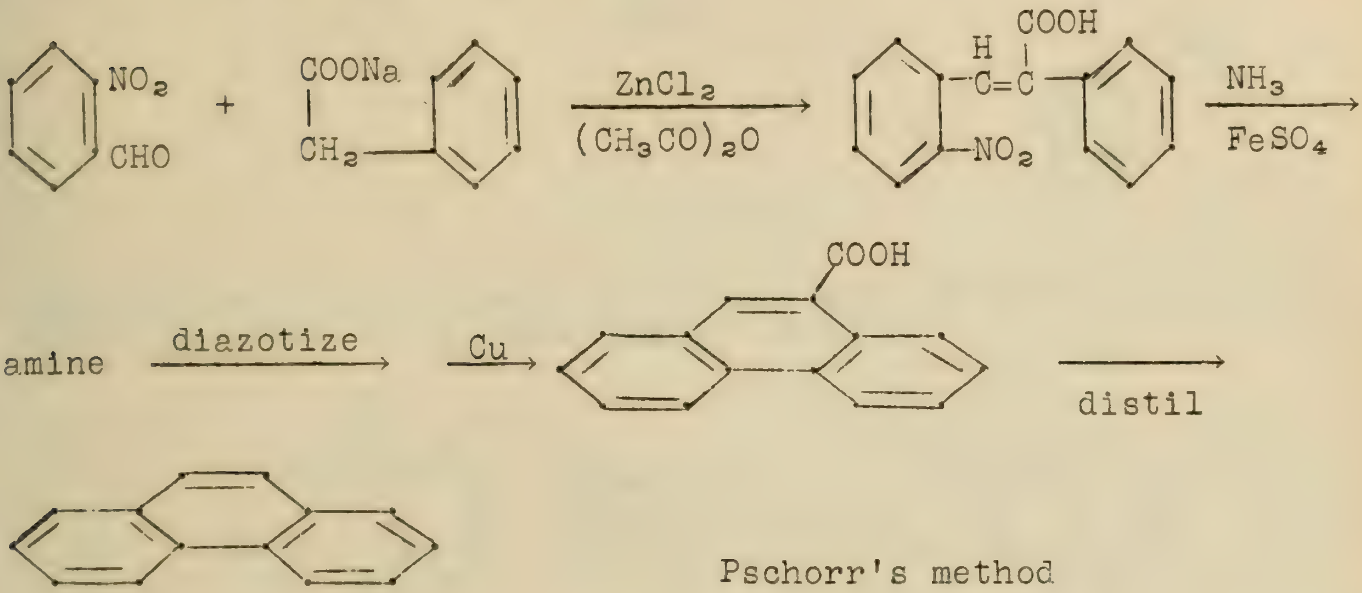
Peak and Robinson, ibid., 1581 (1937).
von Auwers et al, Ber., 32, 3598 (1899); 35, 465 (1902); 35, 4207 (1902).
Woodward, J. Am. Chem. Soc., 62, 1208 (1940).

Reported by John Whitson
March 5, 1941

AROMATIC CYCLODEHYDRATION

Bradsher and coworkers, Duke University

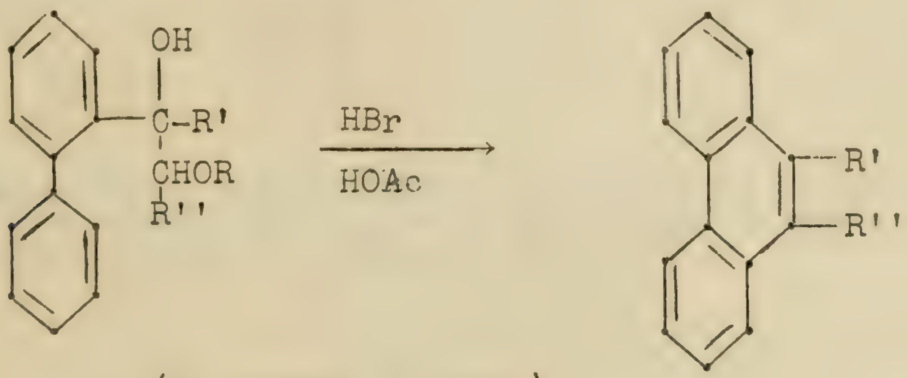
With the exception of Pschorr's method all derivatives of phenanthrene were previously made by dehydrogenation of reduced phenanthrenes. This method is often too destructive to be of much synthetic value.



Pschorr's method

Bradsher has developed a method of synthesizing phenanthrene derivatives by "aromatic cyclodehydration", in which the elements of water are eliminated from a compound with the formation of a new aromatic ring.

Three general cyclodehydration procedures have been used. Method A. An α-(2-biphenyl)-β-alkoxy (or aryloxy) carbinol-1 is cyclized by hydrobromic acid in glacial acetic acid.



(R = alkyl or aryl)

Method B. A 1-(2-biphenyl)-ethylene oxide is cyclicized by hydrobromic acid in glacial acetic acid.

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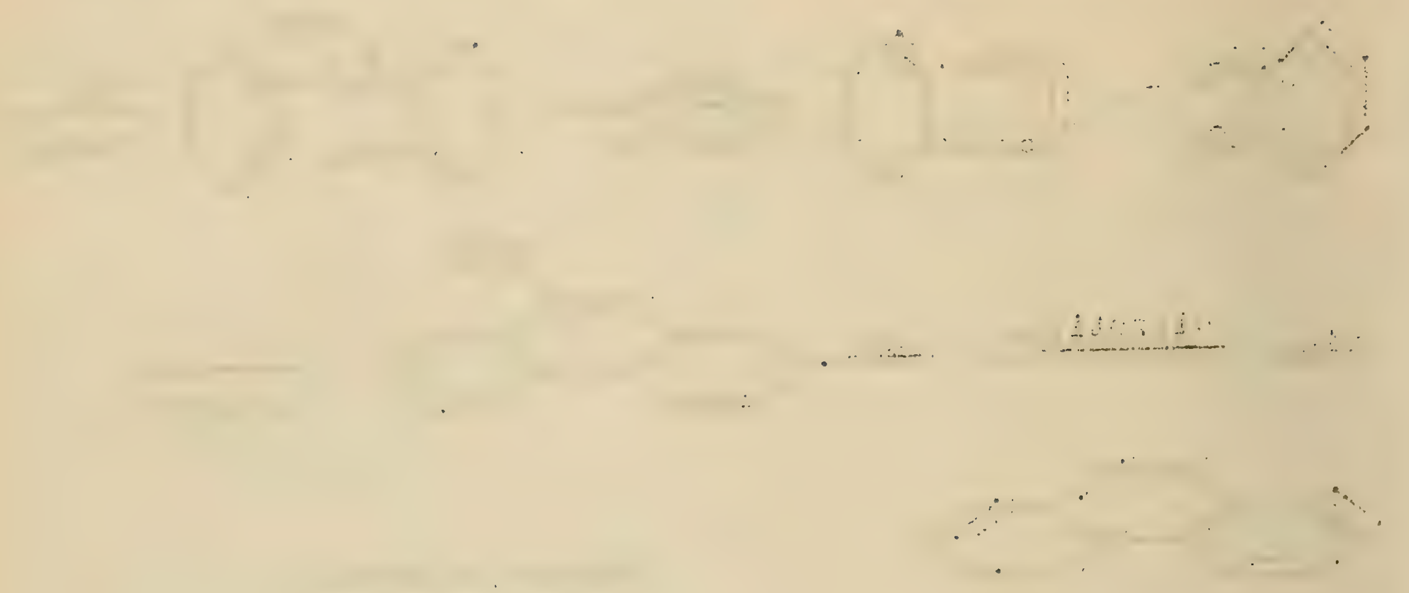

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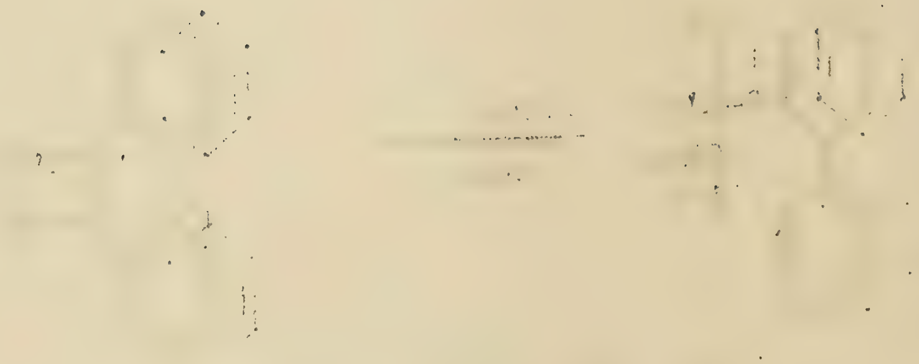

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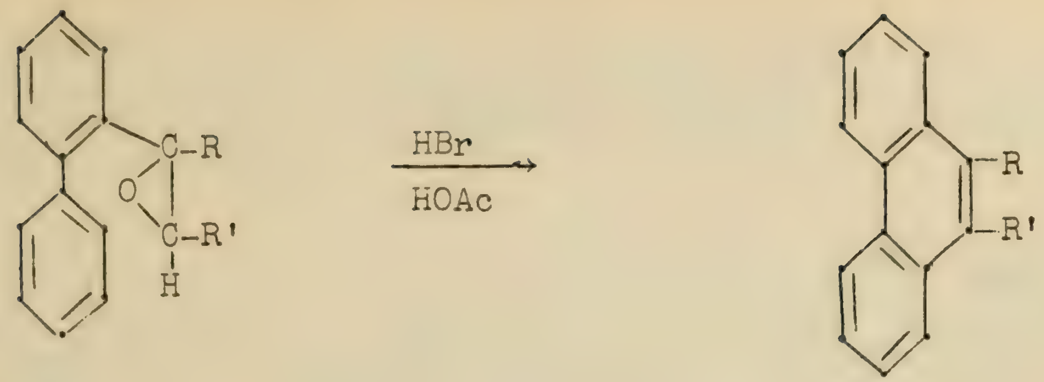
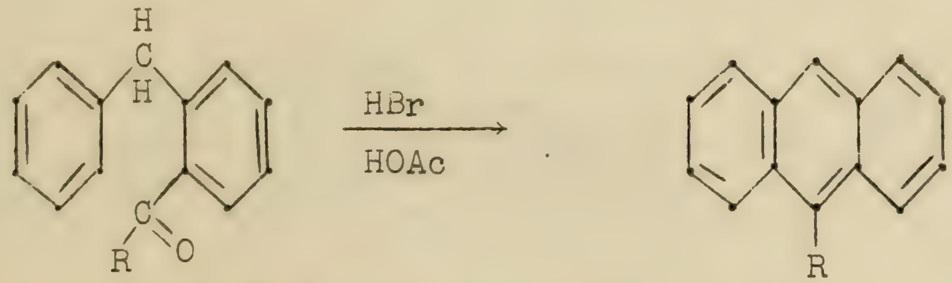
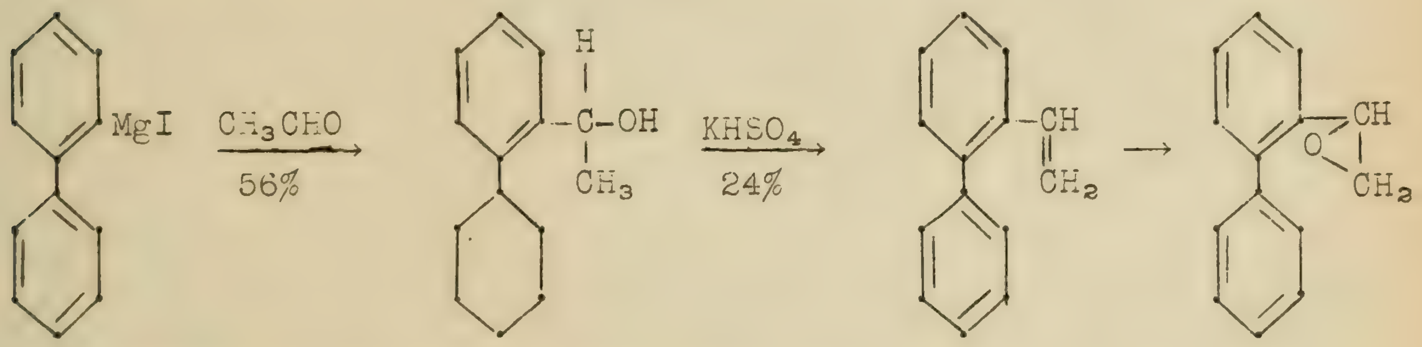


Method C. An *o*-benzylphenyl alkyl (or aryl) ketone is cyclicized by hydrobromic acid in glacial acetic acid.

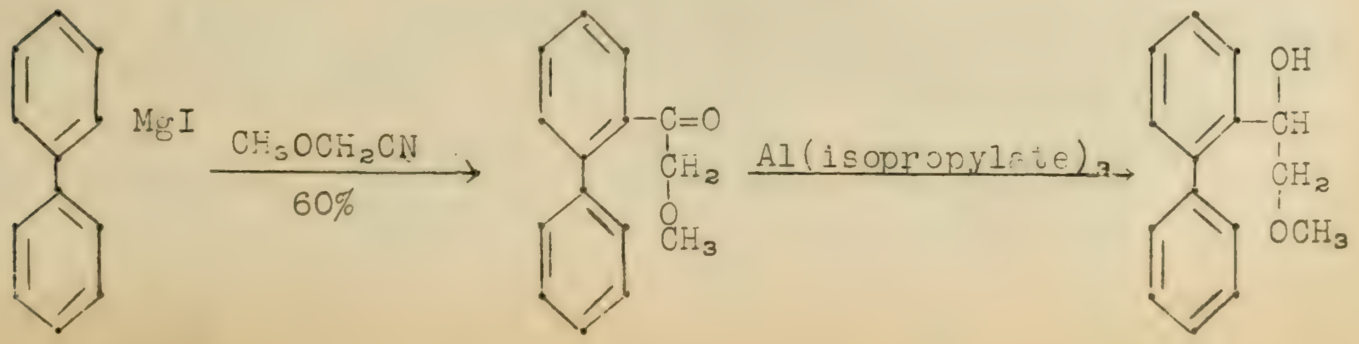


(R = aryl or alkyl)

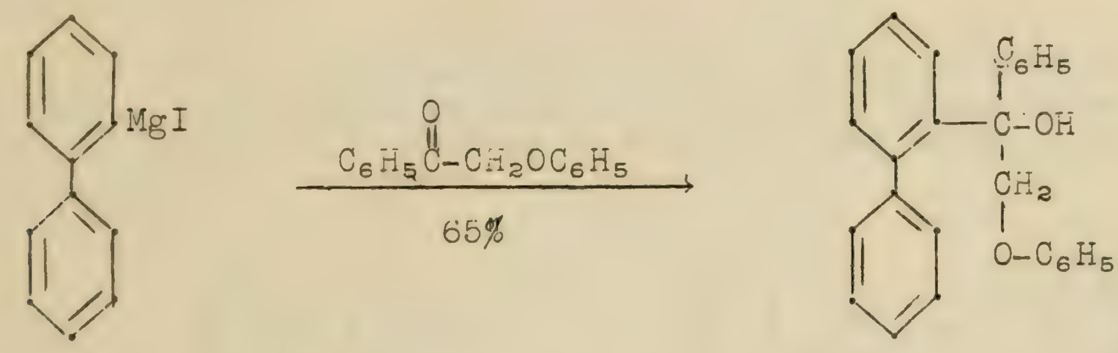
Phenanthrene derivatives without substituents in the central nucleus may be prepared by methods A and B. *o*-Phenylstyrene oxide prepared as shown below was cyclicized by method B to give a very small quantity of phenanthrene.



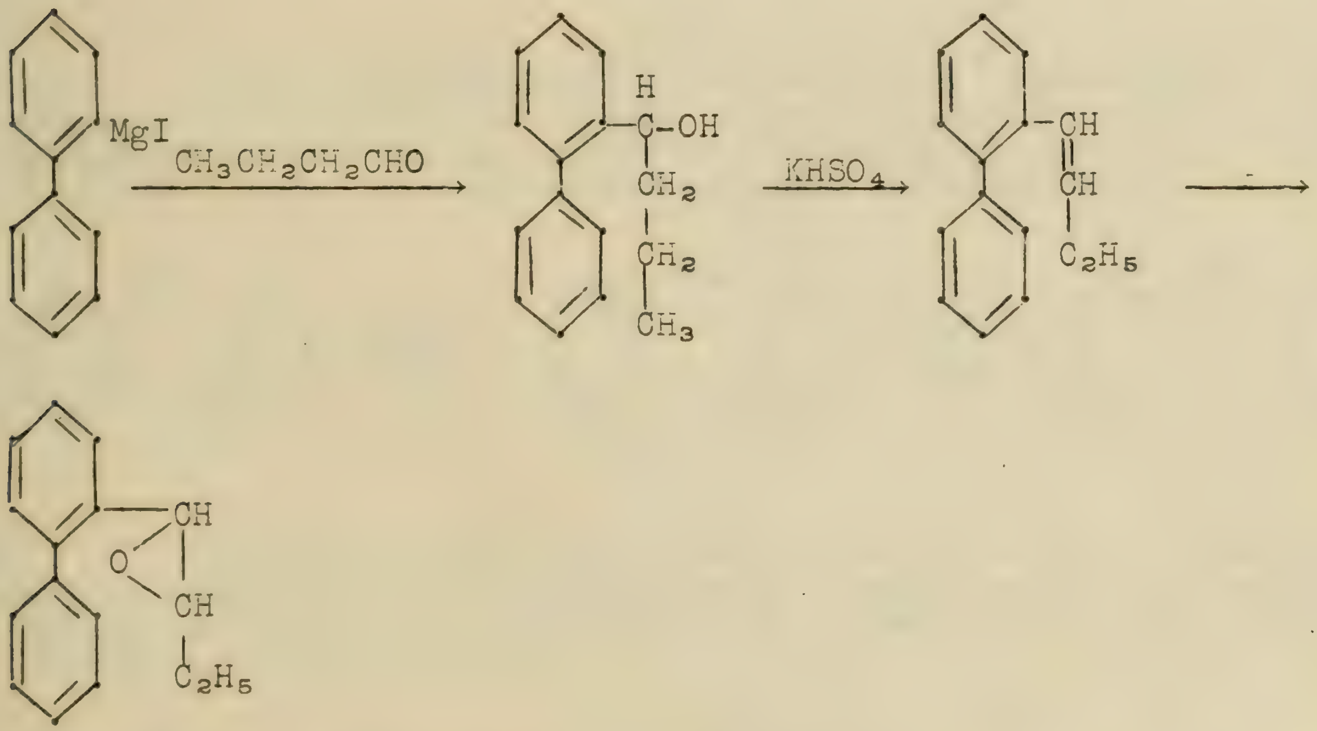
1-(2-Biphenyl)-2-methoxyethanol-1 prepared as shown below was cyclicized by method A to give a 46% yield of phenanthrene based on the 2-(ω-methoxyaceto)-biphenyl used.



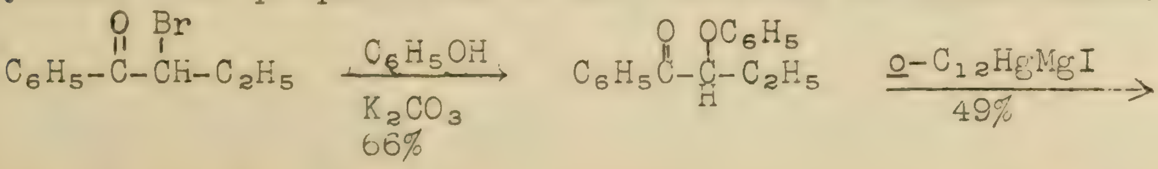
9-Alkyl (or aryl) substituted phenanthrenes can be prepared by methods A and B. 1-Phenyl-**1**-(2-biphenyl)-2-phenoxyethanol-1 prepared as shown below was cyclicized by method A to 9-phenylphenanthrene in 84% yield.



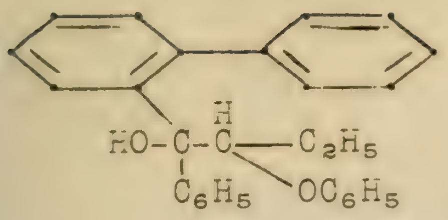
When the phenanthrene is substituted in other than the 9 or 10 position method B gives either a 9 or 10 aryl or alkyl compound. Thus 10 (or 9)-ethylphenanthrene was prepared from 1-(2-biphenyl)-2-ethylethylene oxide in 41% yield on the basis of the aldehyde used. The ethylene oxide preparation is shown below.



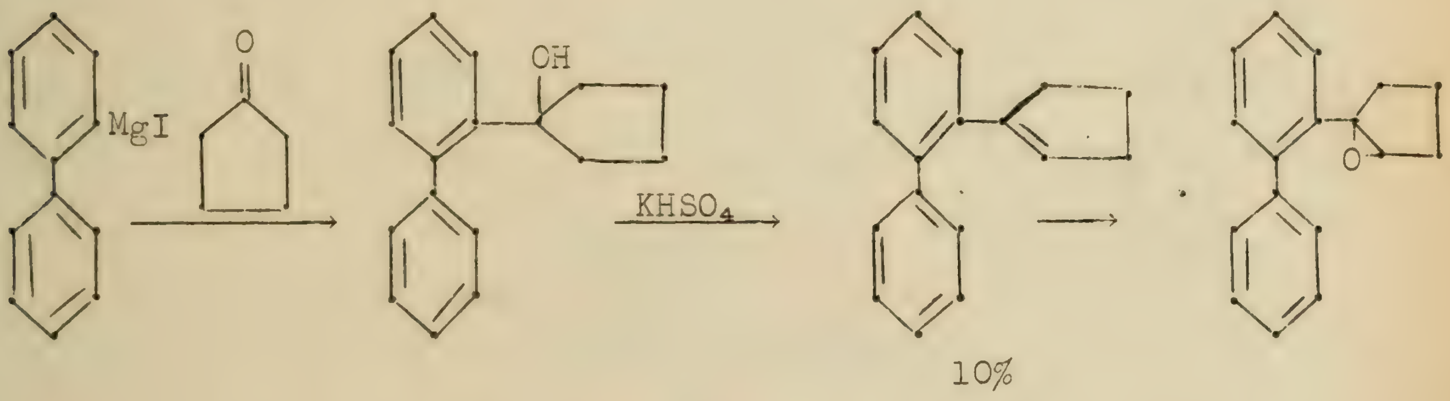
9, 10-Disubstituted phenanthrenes may be prepared by methods A and B. 9-Phenyl-10-ethylphenanthrene was prepared by method A from 1-phenyl-1-(2-biphenyl)-2-phenoxybutanol-1 in 70% yield. The preparation of the carbinol is shown below.



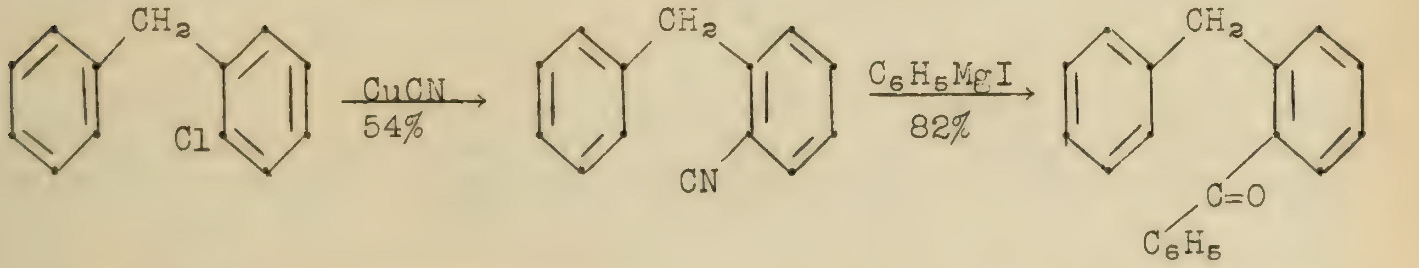
$$C_6H_5-\overset{\overset{O}{\|}}{C}-\overset{\overset{Br}{|}}{CH}-C_2H_5 \xrightarrow[K_2CO_3\ \ 66\%]{C_6H_5OH} C_6H_5\overset{\overset{O}{\|}}{C}-\underset{H}{\overset{\overset{OC_6H_5}{|}}{C}}-C_2H_5 \xrightarrow[49\%]{\underline{o}-C_{12}HgMgI}$$



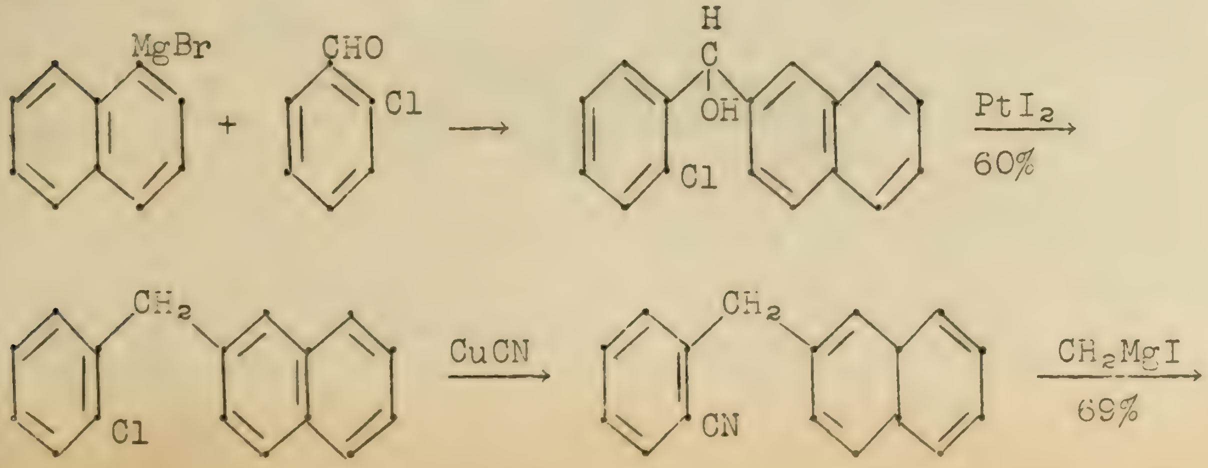
9,10-Cyclopentenophenanthrene was prepared from 1-(2-biphenyl)-cyclopentene oxide by method B in about 17% yield on the basis of the 1-(2-biphenyl)-cyclopentene used. The oxide preparation is as follows:



This cyclodehydration procedure has been extended to the preparation of 9-aryl (or alkyl) substituted anthracenes. Thus o-benzylbenzophenone was cyclicized to 9-phenylanthracene by method C in 75% yield. The ketone was prepared as shown below.



1,2-Benzanthracenes substituted in the 9 or 10-position may be prepared by method C. Thus α-(o-acetobenzyl)naphthalene was dehydrated to 10-methylbenzanthracene in 86% yield. The naphthalene synthesis is as follows:



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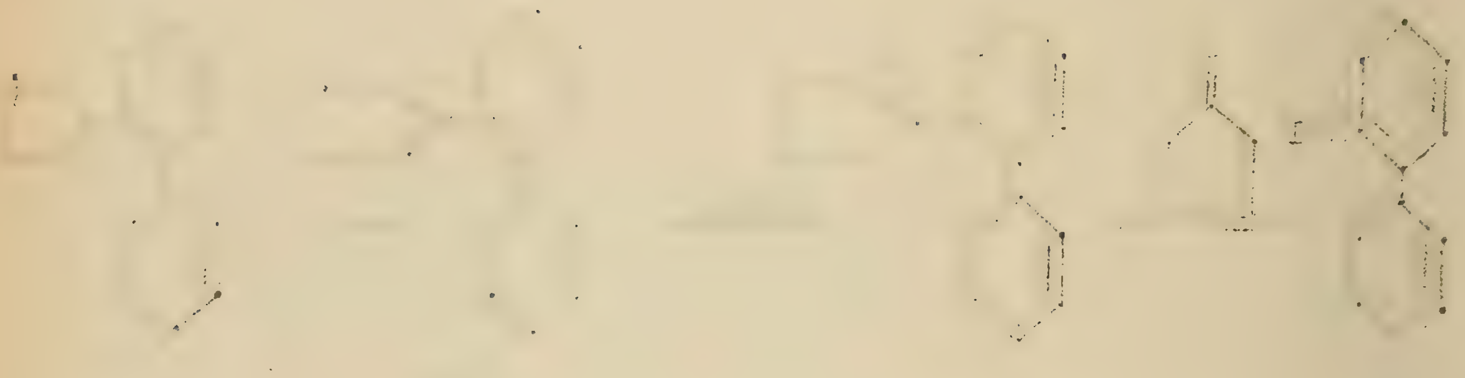

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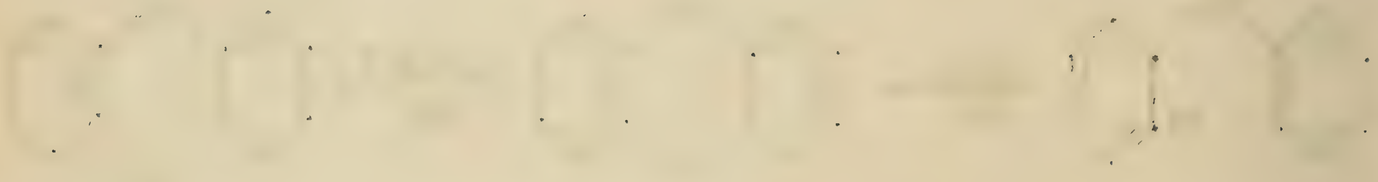

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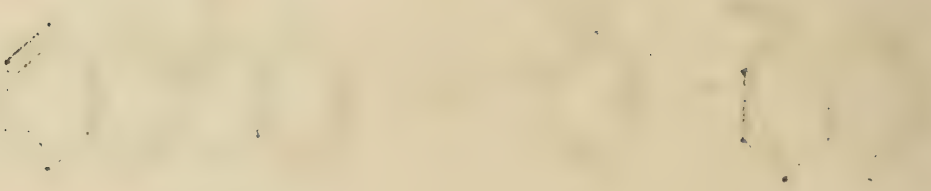
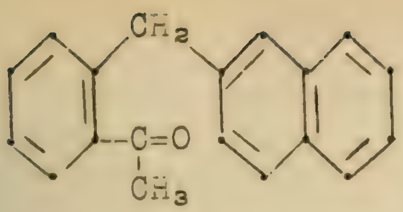
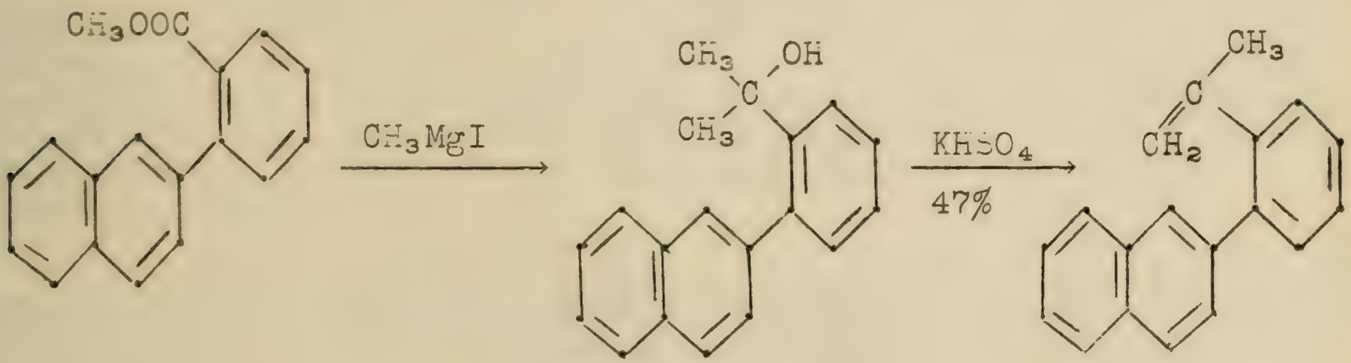


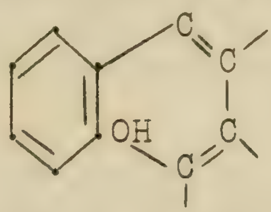


Extension of the method to alkyl chrysenes has been effected by method B. 2'-Isopropenyl-2-phenylnaphthalene was converted to the oxide and this to 6-methylchrysene in 31% yield. The olefin synthesis is shown below.



(not isolated)

As a working hypothesis Bradsher has assumed that in all three methods the common intermediate is the substituted β-(β-styryl)-vinyl alcohol system shown below.



In the general method A the intermediate is thought to be a substituted biphenyl acetaldehyde. Tiffeneau observed that 1-phenyl-2-methoxyethanol-1 is converted to phenylacetaldehyde under conditions comparable to those used by Bradsher.

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Bradsher and Amore, J. Am. Chem. Soc., 63, 493 (1941).
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Bradsher, ibid., 62, 1077 (1940); 62, 486 (1940); 61, 3131 (1939).
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Bradsher and Rosher, ibid., 61, 1524 (1939).
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Tiffeneau, Compt. rend., 145, 811 (1907).

Reported by R. Stephenson
March 12, 1941

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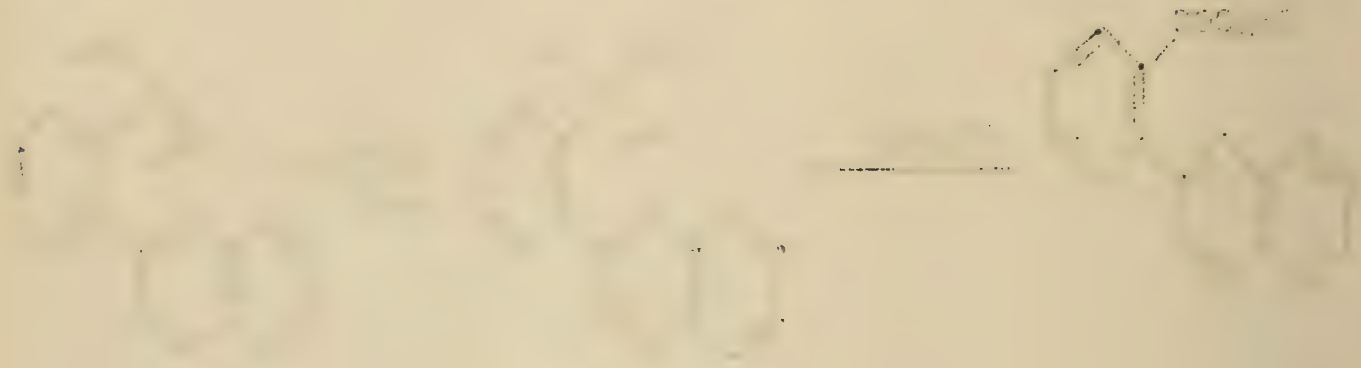

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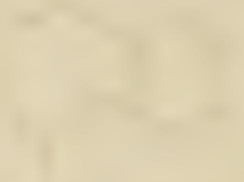

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ADSORPTIVE PROPERTIES OF SYNTHETIC RESINS

S. S. Bhatnagar, University of the Punjab, Lahore, India

I. Introduction

It is generally believed that synthetic resins, like naturally occurring colloids and such artifacts as leather, gelatine, and cellulose derivatives, are not homogeneous, but are composed of macromolecules of varying size.

Barthelemy studied the behavior of colloidal suspensions of phenol-formaldehyde resins and found that acid-condensed resins migrated to the cathode while alkali-catalyzed resins collected at the anode when a small current was passed. The ionic nature of colloids is further revealed by their growth into ionic clusters, a process which probably takes place through the ionic nature of the micro-particles.

This evidence indicates a colloidally disperse structure with a strongly developed inner surface which should show adsorptive properties. Only recently has this field been explored, however, first by Adams and Holmes in 1935. These workers studied the adsorption of many inorganic ions by a variety of polyhydric phenol—formaldehyde resins.

They concluded that these synthetic resins, some of which also occur naturally, were generally superior to recognized adsorbents such as carbon and silica gel. This work is the basis of the new and efficient base-exchange water softeners which are coming into favor in England.

Following the work of Adams and Holmes, Bhatnagar and his students began an intensive study of the mechanism of adsorption by resins.

II. General Laws and Experimental Techniques

The equation deduced independently by Gibbs and Thomson holds quantitatively for adsorption of a purely physical nature such as the sorption of benzoic acid in benzenes by charcoal. This equation is readily derived from thermodynamic considerations and may be expressed,

$$A = -\frac{fc}{RT}\,\frac{ds}{\ln fc}$$

where A is the adsorption per unit surface, s is the interfacial surface tension, and fc is the thermodynamic concentration or "activity."

In 1891 Traube found that organic compounds lower the surface tension of water; he found that, for dilute solutions, the concentrations at which equal depression of the surface tension occurred decreased three-fold for each additional $-CH_2-$ group in any series. This observation, known as Traube's rule, has been stated by Freundlich in terms of adsorption. Thus, as one ascends an homologous series, the adsorption increases regularly.

All the resins were prepared in much the same manner, the procedure being to stir the phenol or aniline with formalin in the presence of HCl or NH_3. The resin was then refluxed with HCl to drive out water, washed thoroughly, dried, and meshed. Adsorption was carried out in carefully cleaned glass-stoppered bottles. Usually one gram of resin was placed in the bottle, 100 cc. of the solution added, and the mixture shaken vigorously for several minutes. After equilibrating for one or two days, portions of the supernatant liquid were withdrawn and analyzed to determine the loss of solute due to adsorption.

III. Studies in Adsorption

Bhatnagar, Kapur and Puri in 1936 began the study of adsorptive properties of acid-condensed phenolic-aldehyde resins in the presence of inorganic acids and bases and aromatic and fatty acids. At this time the effect of concentration of solute was studied and the following observations were recorded:

1. Adsorption follows the Gibbs-Thomson law, and typical adsorption isotherms may be plotted.

2. A solute is likely to be most strongly sorbed from a solvent in which it is not very soluble

3. Alkali hydroxides are much more adsorbed than the carbonates, which in turn are more readily taken up than aniline.

4. Traube's rule holds for aliphatic acids.

5. Inorganic acids are adsorbed preferentially in the order $H_2SO_4 > HNO_3 > HCl$.

6. Sorption of aromatic acids is greater than that of fatty acids.

Three years later Bhatnagar, Kapur and Bhatnagar published the second and third parts of their four part study. The second paper deals with the action of _m_-phenylene-diamine-formaldehyde resins upon varying concentrations of many inorganic potassium salts. The use of an amino resin was suggested by Adams and Holmes work in which it had been proved that cations are adsorbed by phenolic resins, and anions by amino resins. It was hoped to discover an explanation for this behavior, previous theories relating to adsorption and valence, coagulating power, or solubility of solute not being wholly satisfactory.

1. Adsorption _decreases_ with _increasing_ molecular weight with the halides of potassium. This is the opposite of the effect with charcoal.

2. For organic acids the order is oxalic > malonic > succinic > adipic >> formic > acetic > butyric. This is the reverse of the order found for HCl- catalyzed resorcinol-formaldehyde.

3. Adsorption of fatty acids is inversely proportional to solubility.

4. The inverse solubility relationship is considerably beclouded in the case of the ternary salts, $KClO_3$, $KBrO_3$, $KMnO_4$, etc.

In 1938 Tsuruta noted that adsorption of fatty acids by ammonia-condensed phenolic resins decreased as one ascended an homologous series, in violation of Traube's rule. He attributed this behavior to the presence of impurities in the resin. Bhatnagar and his coworkers, however, believed that this effect resulted from the character of the resin pores. Dubinins had previously discovered that very highly activated charcoals have relatively large pores, while less highly activated samples have very fine ultra pores which do not allow large molecules to get into the body of the adsorbent and thereby violate Traube's rule.

The results of the third set of experiments by Bhatnagar, Kapur, and Bhatnagar are presented in Tables I and II. These relations were obtained with m-phenylene diamine-formaldehyde and both acid and base-condensed phenolic resins.

TABLE I

Acid	Ionization Constant	% Adsorption by 1 g. of resin from 100 cc of aqueous solution		
		Phenol-HCl Catalyzed	Phenol-NH_3 Catalyzed	Phenylene Diamene
Formic	2.1×10^{-4}	2	27	40
Acetic	1.8×10^{-5}	5	23	37
Butyric	1.5×10^{-5}	9	14	28
Oxalic	3.8×10^{-2}		60	88
Malonic	1.6×10^{-3}		47	86
Succinic	6.6×10^{-5}		38	74
Adipic	3.7×10^{-5}		31	70

Table I shows the reversal of Traube's rule with basic resins and also shows that basic resins are much better adsorbents than acid-catalyzed materials.

Both tables indicate a fair correlation between ionization and adsorption, the principle exception being hydroxyacetic acid in Table II. The depressing effect of the hydroxyl group upon adsorption is well known, however, and appears potent enough here to overcome the influence of ionization.

TABLE II

Influence of Substituents and Ionization on Adsorption

Acid	Ionization Constant	Dipole Moment of substituent groups x 10^{18}	% Adsorption by 1 g. of m-phenylenediamine resin from 100 cc. of aqueous solution
Acetic	1.8×10^{-5}		37
Chloracetic	1.5×10^{-3}	2.0	61
Dichloracetic	5.0×10^{-2}	4.0	77
Trichloracetic	2.0×10^{-1}	6.0	84
Phenylacetic	5.5×10^{-5}		73
Cyanacetic	3.6×10^{-3}	3.5	66
Hydroxyacetic	1.5×10^{-4}	1.7	31
Aminoacetic	3.4×10^{-10}	1.3	8

Part four of the research consists largely of an amplification of the ideas presented previously and these will be discussed later. Experiments were carried out, however, in which the type of resin and dipole moment of the solvent were varied. It was shown that -

1. In non-polar solvents Traube's rule is reversed even for acid-catalyzed resins.

2. Per cent sorption increases with increasing dipole moment of the solvent.

IV. Theories and Explanations

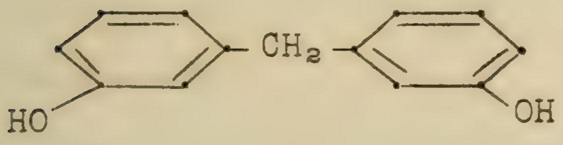
The development of a complete explanation of adsorption by resins is rather interesting. In the first paper in 1936, Bhatnagar and his coworkers confined themselves mainly to experimental observations. It was believed that basicity of inorganic acids and the nature of the anions influenced their adsorption slightly.

In part two, 1939, it was thought that solubility of the solute in solvent, and to a greater extent, molecular weight, was the deciding factor. Valence was ruled out at this point. The high

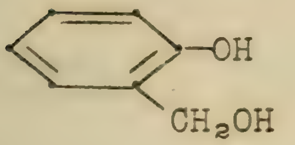
sorption of $KMnO_4$ was probably due to chemical reaction. The reversal of Traube's rule with phenylenediamine resins was observed but no explanation had yet been advanced. Tables I and II show the weakness of this theory. In part three the work became more theoretical and the explanation was sought within the nature of the resin itself. Alkalies are known to be more effective condensing agents and, therefore, produced resins with finer pores and larger surfaces. Although these basic resins adsorbed more effectively than those from acid catalysis, sorption falls off as one ascends a series in consequence of increased size of adsorbate molecules. These ideas correspond to the evidence presented by Dubinins on charcoal. Adsorption appeared then to be determined by two forces, (1) surface forces which alone govern the adsorption of acids by acid-condensed phenolic resins according to the Gibbs-Thomson law, and (2) forces arising from the physico-chemical action of protons on the basic resins. The second force overshadows the former in the case of acids and basic resins. Here the ionization of the acid seemed to be the controlling factor once the solute had penetrated to the resin surface. This theory fails to explain why the dibasic acids (relatively well ionized) are less adsorbed than the monocarboxy acids by HCl- catalyzed phenolic resins.

In part four the Langmuir-Harkins theory of surface orientation is applied to form an explanation of all the phenomena observed. According to this theory the polar portion of an acid, -COOH, is attracted to or dissolved in the most polar part of the solutions.

Megson and Drummond had previously isolated



from the HCl- catalyzed condensation of phenol with formaldehyde, and had obtained alcohols of the type,



from alkaline condensation. This indicates that the acid-catalyzed resin is less polar than water while the alkali-condensed resin is highly polar.

At a water-base condensed resin interface the resin is more polar and attracts the -COOH of the fatty acid. As the size of the alkyl group is increased it becomes increasingly difficult for the -COOH- resin attraction to bring the alkyl group into the resin, hence the adsorption decreases, and Traube's rule is violated. Furthermore, molecular association decreases as we ascend the acid series and the molecules tend to spread out over the resin instead of being held in molecular clusters by a single -COOH group. This obviously decreases the weight of acid adsorbed.

With a water solution of an acid condensed phenolic resins (or whenever the solvent is more polar than the resin) the -COOH group is oriented toward the water, the alkyl group being pointed toward the resin part of the interface. As the alkyl group

is made larger the tendency of the entire molecule to stick to or be dissolved in water decreases and we observe the normal increase in adsorption with increasing molecular weight.

Proof of this theory is found in Table III where the cis form of the acid is more strongly adsorbed by basic resins and less so by acidic.

TABLE III

	% Adsorption		
Acid	HCl-Phenolic resin	NH_3-Phenolic resin	*m*-phenylene-diamine resin
Fumaric	2.6	27	71
Maleic	2.0	43	81

Table I shows the adsorption of oxalic and malonic acids is just double that of formic and acetic, probably because each of the former has a -COOH group in place of one hydrogen.

Table II shows that as more polar groups are introduced into the molecules, the adsorption increases with basic resins. Since the $-NH_2$ group has a moment opposite to that of other groups, the decrease of adsorption in the case of amino acids is also explained satisfactorily.

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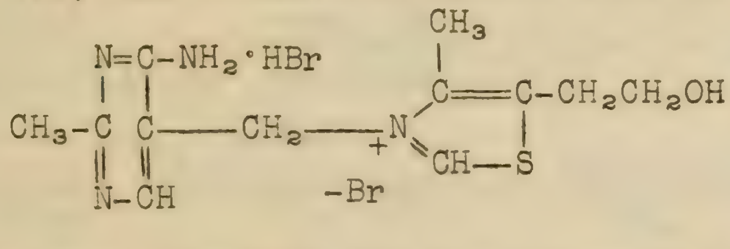
Reported by J. Wayne Kneisley
March 12, 1941

STUDIES IN THE PYRIDINE SERIES

Elderfield - Columbia University

The determination of the structure of vitamin B_1, thiamine (I), has occasioned recent work on new pyridine derivatives.

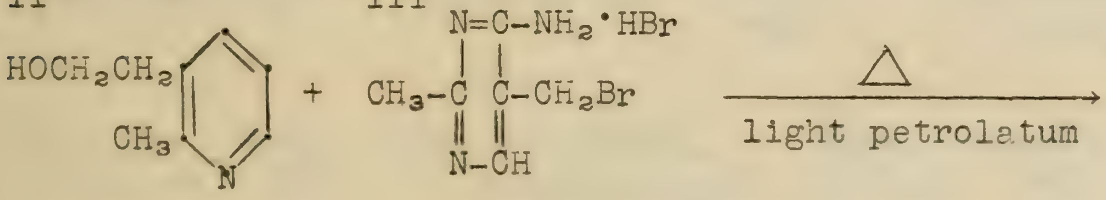
I



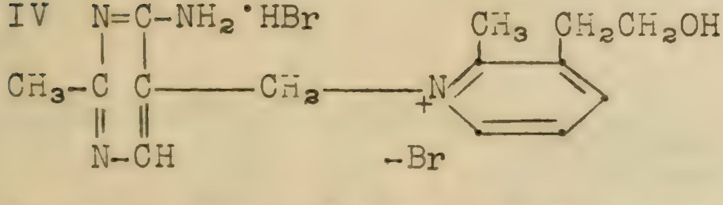
One of the ways in which the structure of thiamine may be modified in attempts to correlate structure and physiological activity is by replacement of the thiazole portion of the molecule by an appropriately substituted pyridine group. According to Erlenmeyer's theory of isosterism, the substitution of a -CH=CH- unit for the sulfur atom of the thiazole portion should result in a compound very similar in its chemical and physiological activity to vitamin B_1 itself. This compound has been made (IV), as well as several other similar ones in which the substituents on the pyridine nucleus are slightly modified. Since no significant results have as yet been published on the physiological action of these compounds, this report will be concerned with the synthetic work only.

In order to obtain the pyridine analogue (IV), or isoster, of thiamine, it was necessary to condense 2-methyl-3-(β-hydroxyethyl)-pyridine (II) with the pyrimidine component (2-methyl-4-amino-5-bromomethylpyrimidine, III) of thiamine.

II III

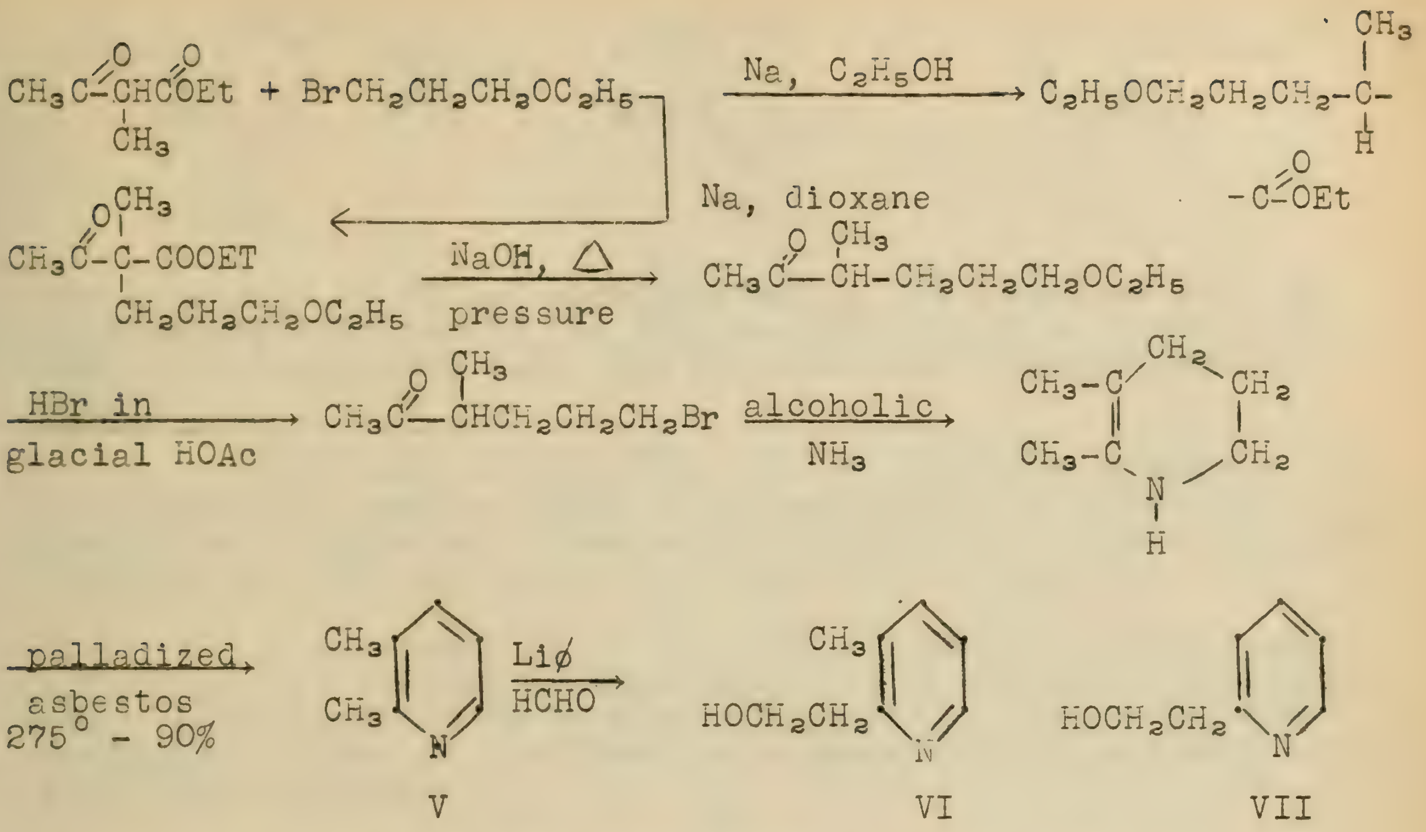


IV



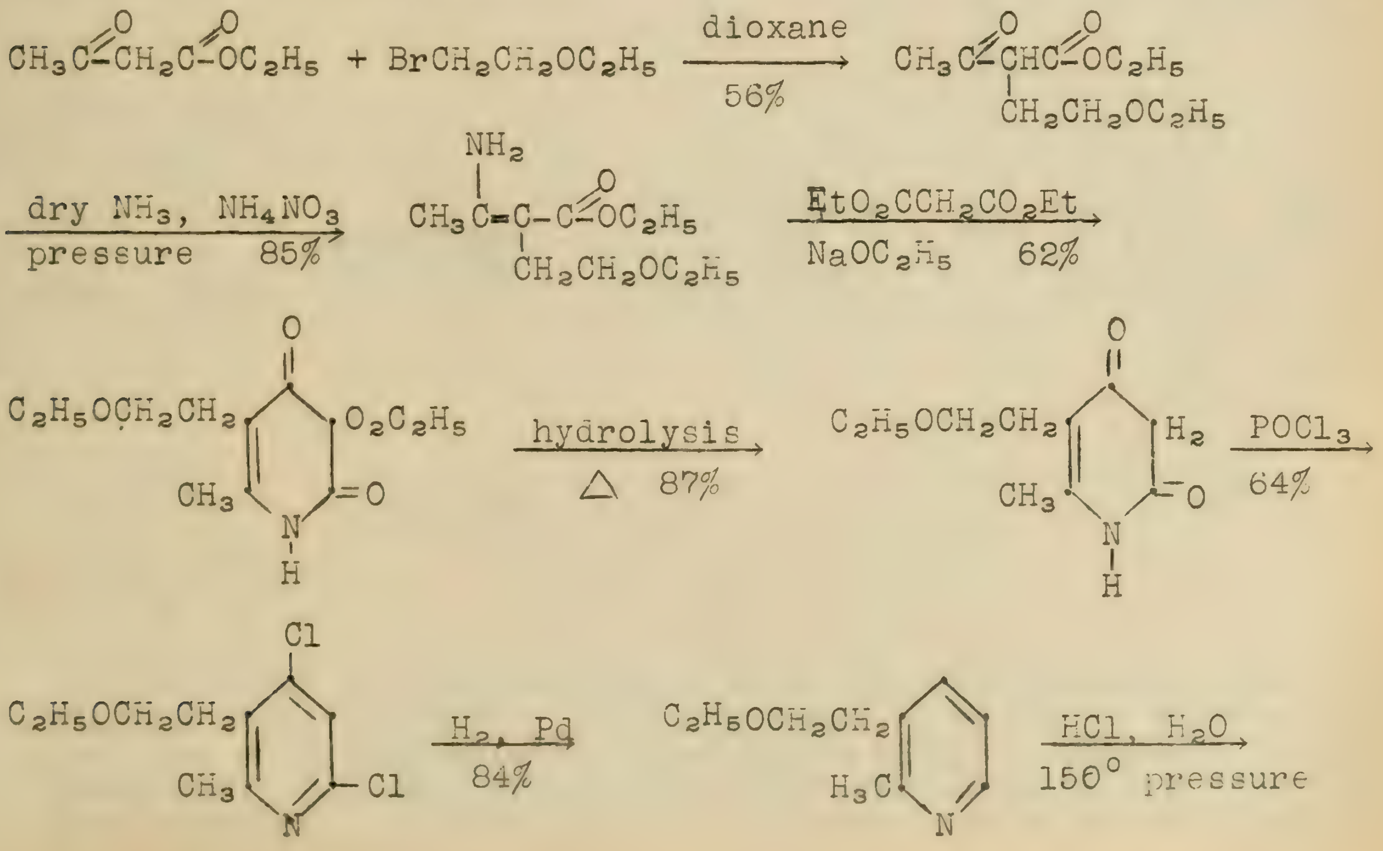
Since the pyrimidine component was available, the chief concern became the synthesis of compound II, as well as similar 2,3-disubstituted pyridines.

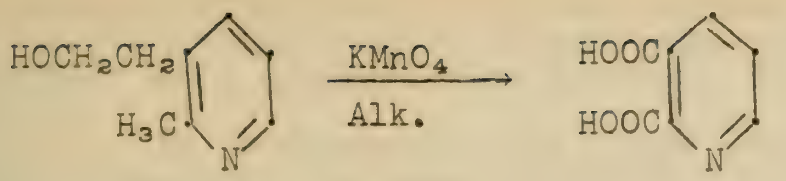
The first of these pyridines prepared was 2-(β-hydroxyethyl)-3-picoline (VI). Since this compound was obtained by reaction of formaldehyde on 2,3-dimethylpyridine (V), it became necessary to devise a satisfactory method of preparation for the latter compound. The entire synthesis is as follows:



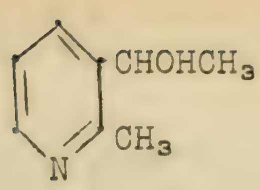
(The yields were about 50-60% in all steps except the dehydrogenation.) 2-(β-Hydroxyethyl)-pyridine may be prepared from 2-picoline by a similar condensation with formaldehyde.

The desired 2,3-disubstituted pyridine (II) was synthesized as follows:





II VIII

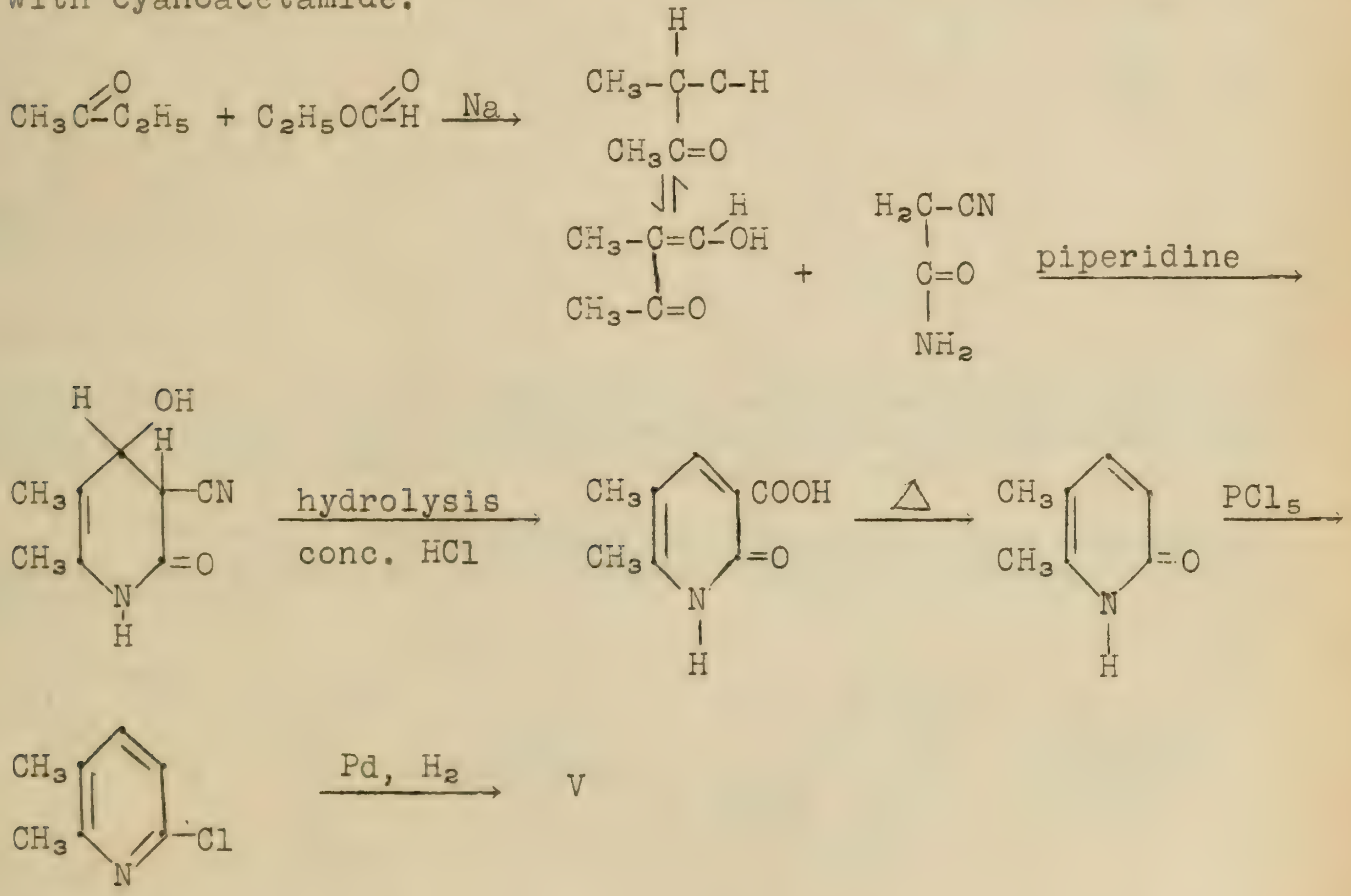


IX

The structure of II was corroborated by the formation of a p-nitrobenzoyl derivative, by its non-identity with 2-methyl-3-(α-hydroxy)-pyridine (IX), and by oxidation to quinolinic acid (VIII).

Compounds II, VI, VII, and IX have been condensed with the pyrimidine portion (III) of thiamine to give molecules analogous to thiamine. Some anti-polyneuritic activity has been reported in the case of the compound derived from IX.

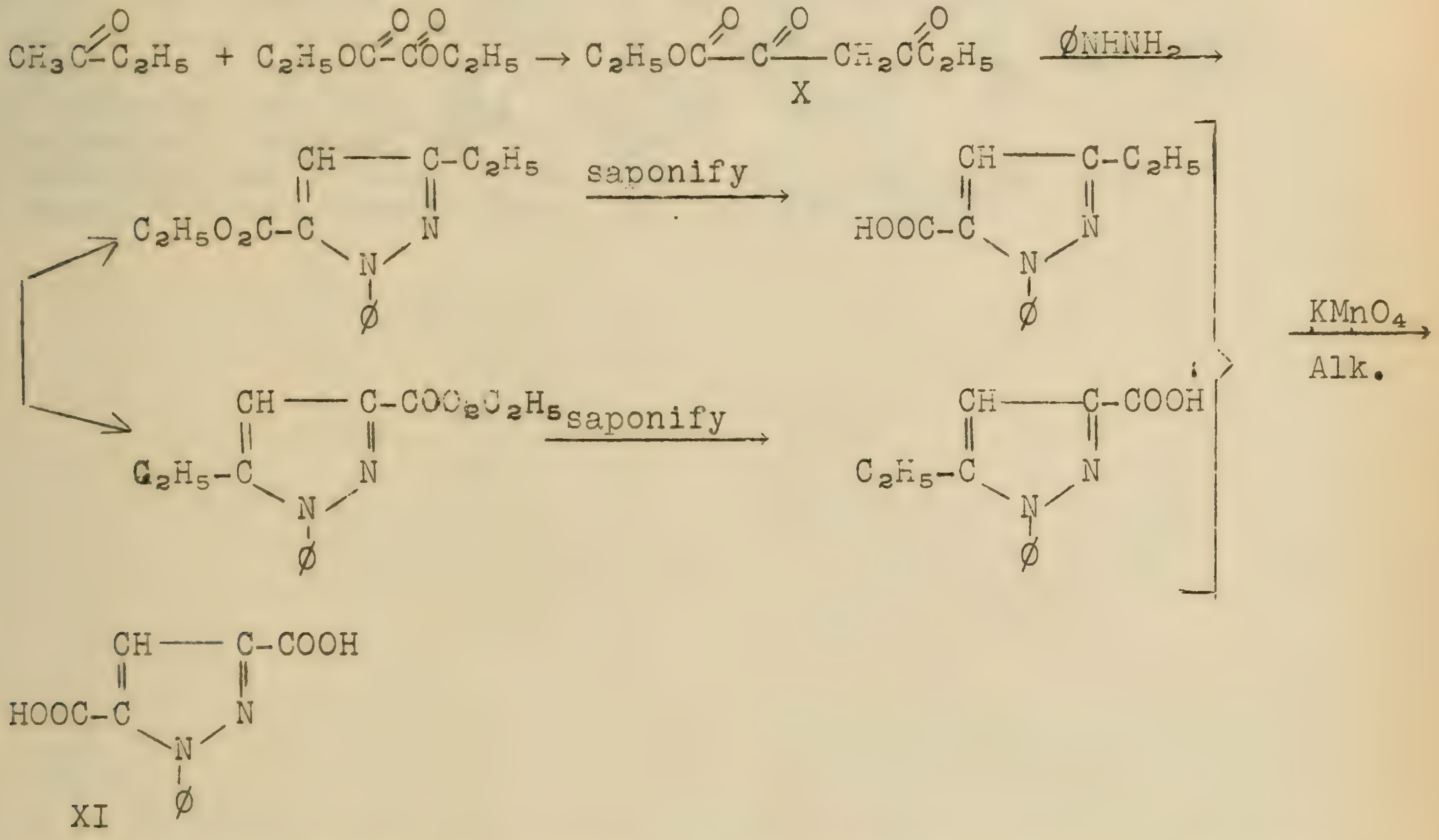
In continuation of his work on pyridine derivatives, Elderfield has devised another synthesis of 2,3-dimethylpyridine (V). This may prove to be a general method of preparing 2,3-dialkylpyridines; it involves the condensation of α-formyl ketones with cyanoacetamide.



The formation of 2,3-dimethylpyridine by this method is taken as evidence that the formyl group is taken on by the methylene rather than the methyl group of methylethyl ketone, in the first condensation. Had the reverse been true, 2-ethylpyridine would have been obtained. If methyl-γ-ethoxypropyl ketone is used in place

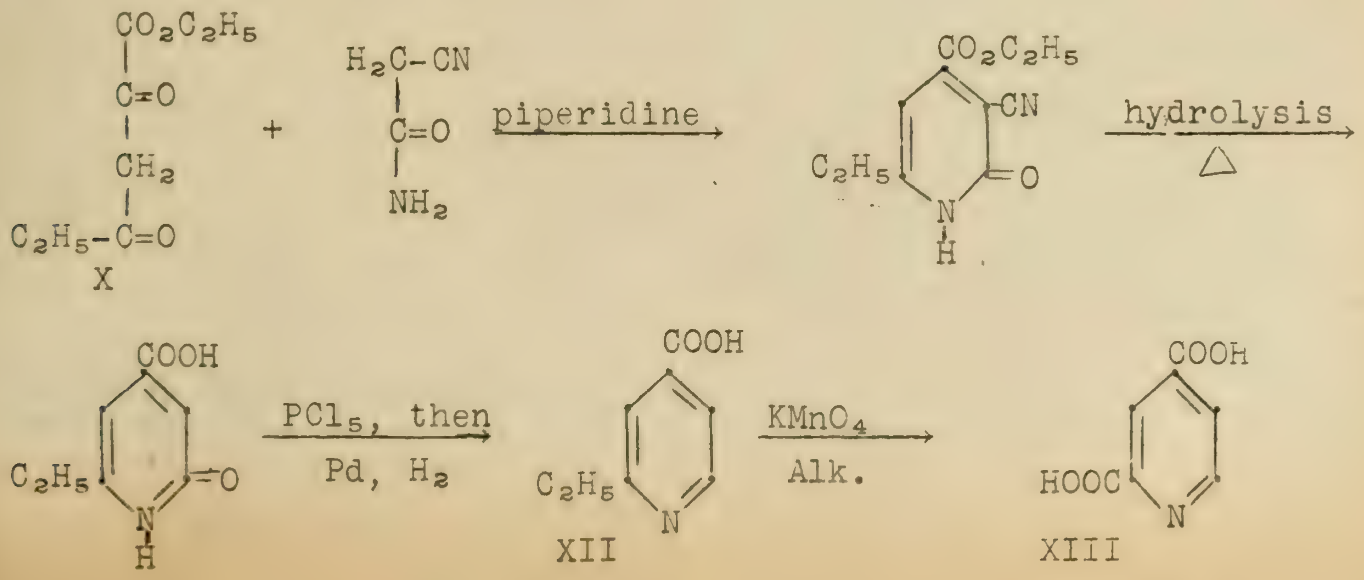
of methylethyl ketone, the formyl ketone resulting from the condensation with ethyl formate polymerizes rapidly; thus, this method is worthless as a synthesis for compound II.

It is noteworthy that when ethyl oxalate is substituted for ethyl formate in the above reaction, the condensation takes place on the methyl group instead of the methylene. This was demonstrated by the following reactions:



If condensation had taken place on the methylene group, the final product would have been 1-phenylpyrazole-3,4,5-tricarboxylic acid instead of 1-phenylpyrazole-3,5-dicarboxylic acid (XI).

The ethyl propionylpyruvate (X) formed by the above condensation may be used in the synthesis of 2-ethylisonicotinic acid (XII) as follows:



The position of the substituents in compound XII was confirmed by oxidation to lutidinic acid (XIII).

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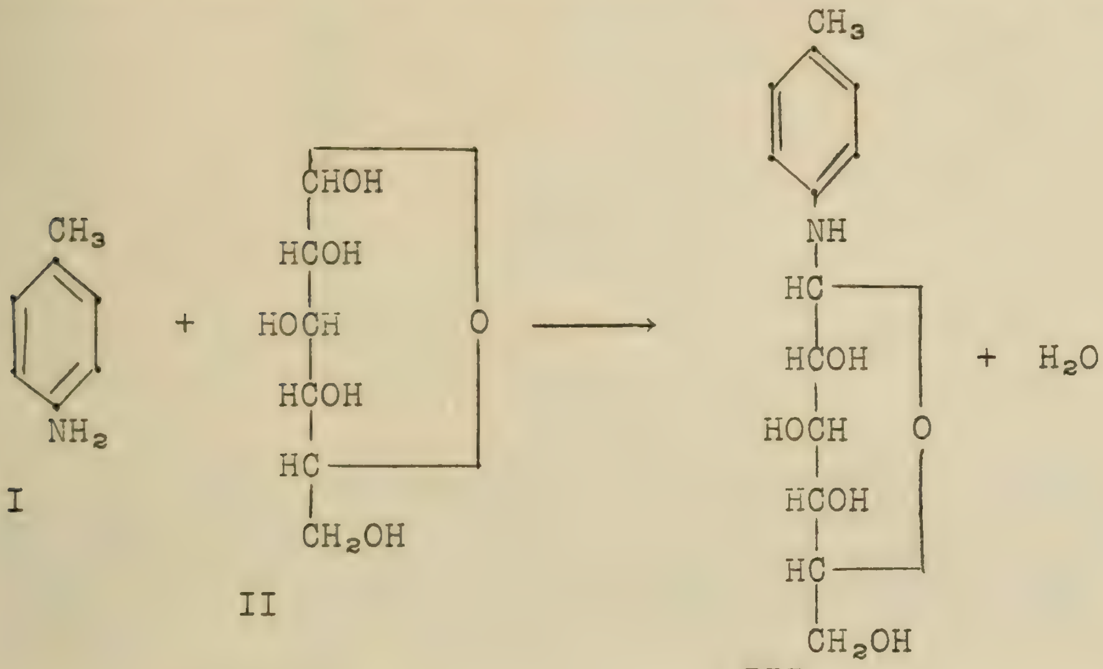
Reported by P. B. Welldon
March 19, 1941

N-GLYCOSIDES

Friedrich Weygand - Kaiser Wilhelm Institute of Medicine,
Institute of Chemistry, Heidelberg.

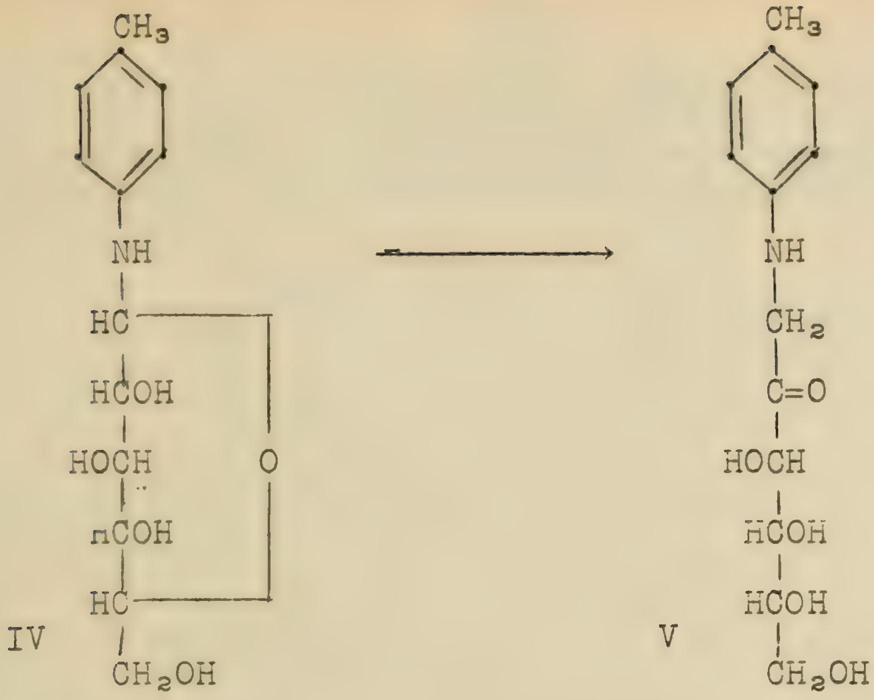
Aryl amines, such as aniline, *p*-toluidine, *p*-phenetidine, 3,4-dimethylaniline, etc., can be condensed with aldoses, such as glucose, mannose, xylose, arabinose, etc., to give N-glycosides.



I II III

A general procedure which produces good yields of pure products was developed by Weygand, and consists in heating with shaking 1 mol sugar and 1.1-1.4 moles amine with 2-4 moles water, in a boiling water bath. A homogeneous solution is obtained in 2-15 minutes, and after the reaction is completed by a few minutes additional heating, alcohol is added and the solution cooled. The N-glycoside crystallizes as a snow-white product, is filtered and washed with ether, and rarely requires further purification.

N-Glycoside formation was studied by Irvine and Gilmour, in 1906, who heated *p*-phenetidine and glucose in 83 per cent alcohol and isolated a crystalline compound. Amadori, in 1925-31, did considerable work on this subject, and found that actually two compounds were formed from the sugar and the amine. The first was formed by heating the amine and sugar in alcoholic solution, and the second by fusing the reactants with no solvent present. These reactions were not clean-cut, and both products were found in either case, with one predominating. In general, it was found that the first product was formed at lower temperatures than the second, and was unstable toward acids, whereas the second was stable toward acids and unstable toward alkalis. The second compound was formed at higher temperatures and also by prolonged heating of the first. Amadori considered the second to be a Schiff base, but extensive work by Kuhn and Weygand in 1937, proved it to be an aryl-*d*-isoglycosamine. The "Amadori rearrangement" of *p*-toluidine *d*-glucoside (IV) to N-*p*-tolyl-*d*-isoglucosamine (V) illustrates this:


IV

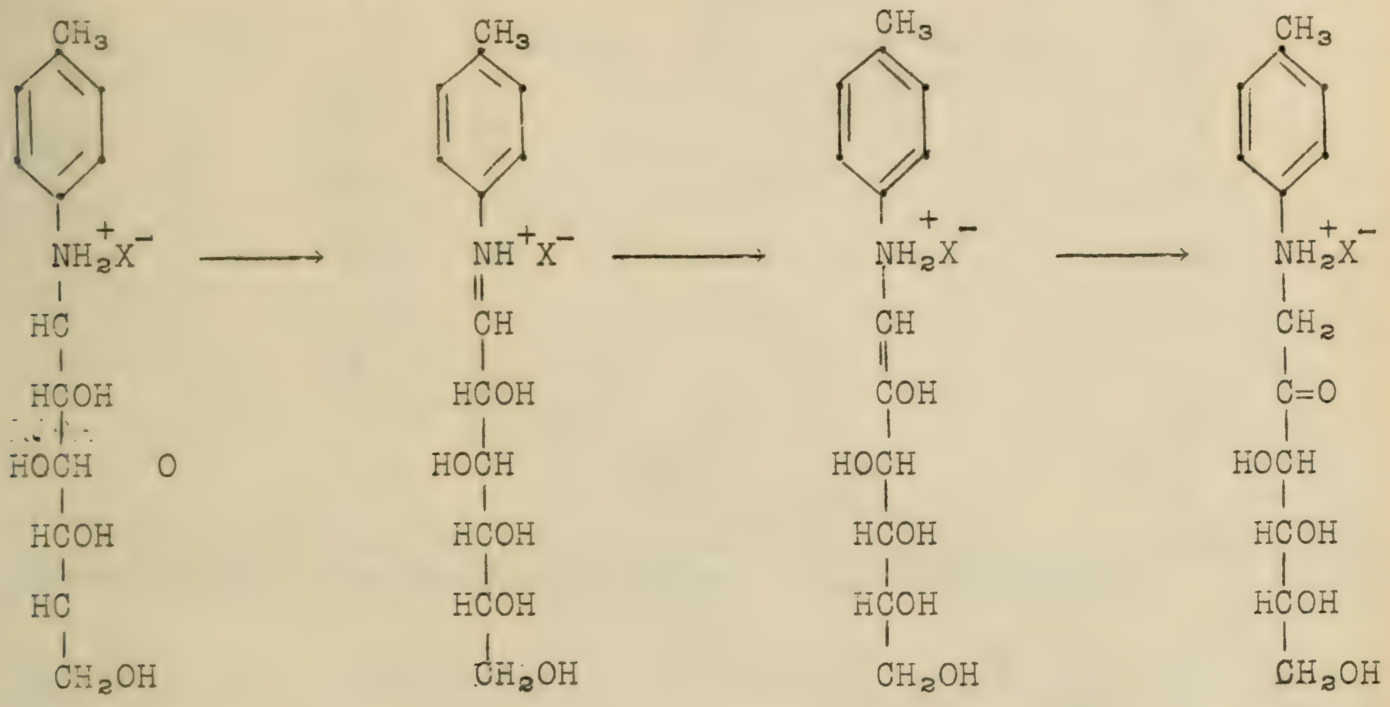
V

The decision that the rearrangement product was *p*-tolyl-*d*-isoglucosamine was based on (1) the catalytic hydrogenation of the product which gave not the expected N-*p*-tolyl-*d*-glucamine, but N-*p*-tolyl-*d*-mannamine, (2) the formation of an oxime, (3) the great stability toward acid, which effects no simple hydrolysis, and (4) mutarotation.

Both N-glucosides and aryl-isoglucosamines reduce hot Fehling and cold silver-ammonia solutions, but the isoglucosamines only will reduce *o*-dinitrobenzene solution. The N-glucosides melt with decomposition and effervescence, differing in this respect from the isoglucosamines.

Mention has been made above of only the glucose derivatives. Curiously enough, the Amadori rearrangement was found to take place only on N-glycosides having glucose as the sugar component and *p*-toluidine, *p*-phenetidine, *p*-anisidine or 3,4-dimethylaniline as the amine involved. Weygand, in very recent work (1940), looked for the cause of this exceptional behavior of glucose. He ran into a series of inconsistent results; sometimes the Amadori rearrangement took place on a N-glycoside, sometimes not, and yields on one rearrangement reaction varied widely. He finally found the trouble to be involved in a catalytic effect by acids or acid-reacting salts. Pure *p*-phenetidine *d*-glucoside, for example, will not rearrange on prolonged heating, although earlier work by Kuhn and Birkofer reported this as being accomplished. Weygand attributed their successful rearrangement to acid impurities in the reaction, and went on to show that the Amadori rearrangement not only took place more easily and quickly, and gave better yields, when catalyzed by a small amount of acid, but the rearrangement was no longer restricted to glucosides-xylosides, arabinosides, rhamnosides, mannosides and galactosides were successfully rearranged to the corresponding isoglycosamines.

The general mechanism of the Amadori rearrangement is postulated as an allylic rearrangement of a Schiff base to an enol, with subsequent ketonization. Since the rearrangement is acid-catalyzed, the mechanism is best represented as taking place through intermediate cations:

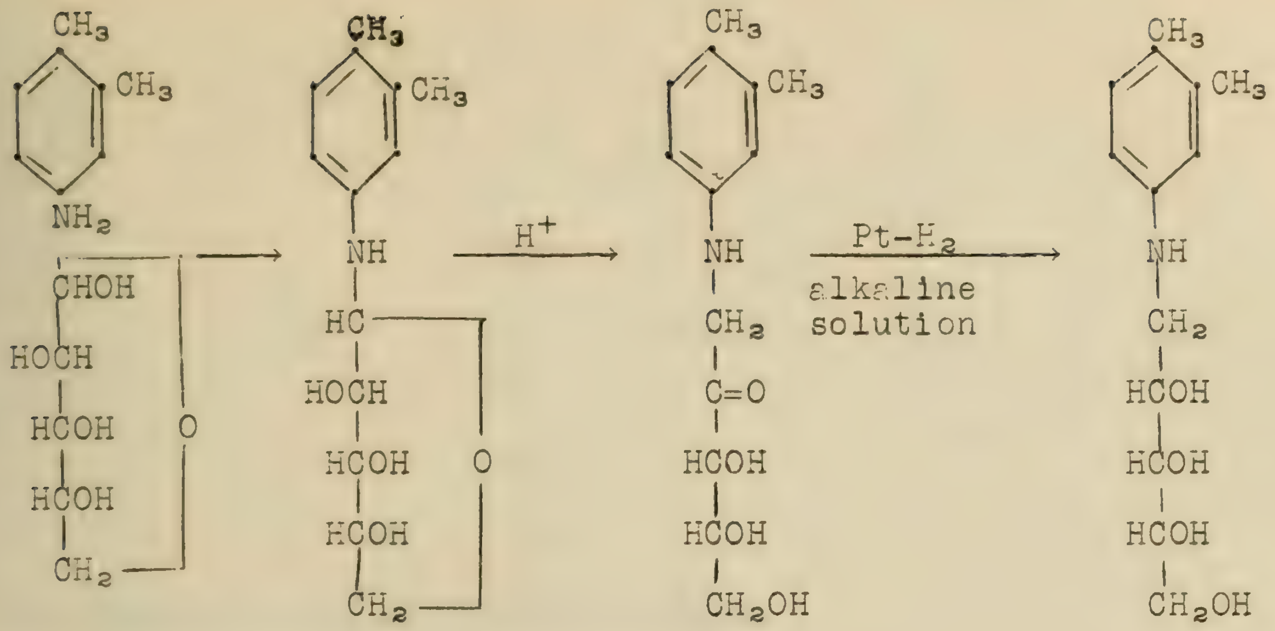


It has not been determined as yet whether an equilibrium is set up between glycoside and isoglycosamine in the Amadori rearrangement.

Several miscellaneous studies on N-glycosides and the corresponding isoglycosamines are of interest.

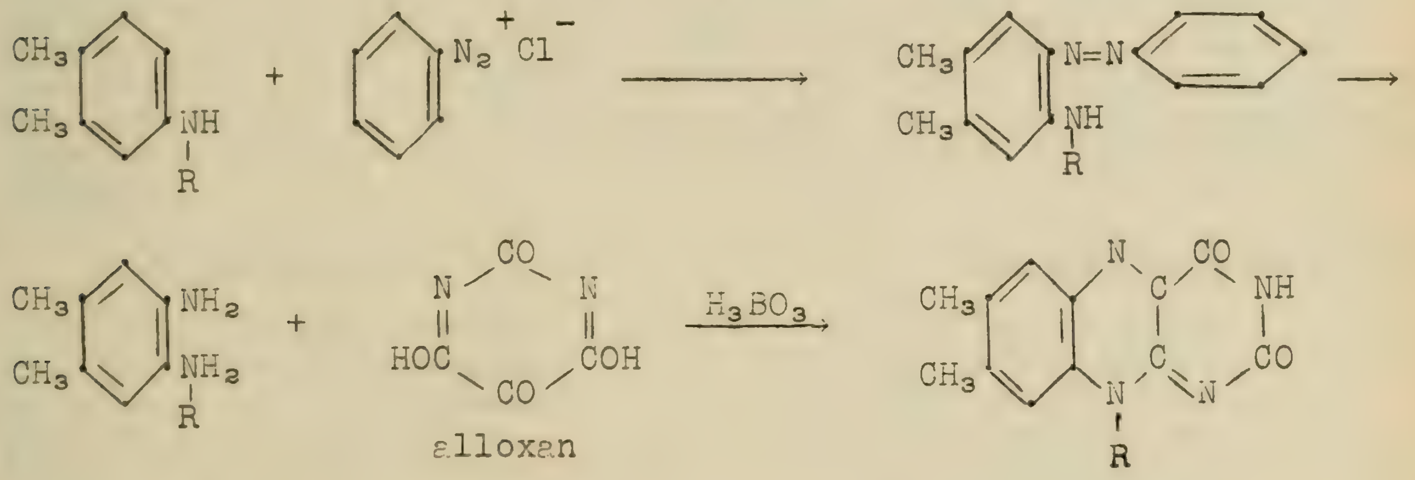
1. Synthesis of lactoflavin - Vitamin B_2

The accepted structure for vitamin B_2 is IX, 6,7-dimethyl-9-d-ribitylisoalloxazine. Up to now, the only method for obtaining the intermediate ribityl compound used in the synthesis of vitamin B_2 has been from d-ribose itself. The natural sources of d-ribose are rather meager, and it must for the most part be prepared from d-arabinose or d-arabonic acid, in 10-17 per cent yield, the preparation requiring several days. If d-arabinose (VI) and 3,4-dimethylaniline are condensed in the presence of a little acid, the reaction goes smoothly, and the Amadori rearrangement takes place quickly at 75°. The resulting 3,4-dimethylphenyl-d-isoarabinosamine is then hydrogenated in alkaline solution with Adams platinum catalyst, giving 3,4-dimethylphenyl-d-ribamine (VIII) in about 13 per cent yield, based on the original d-arabinose.

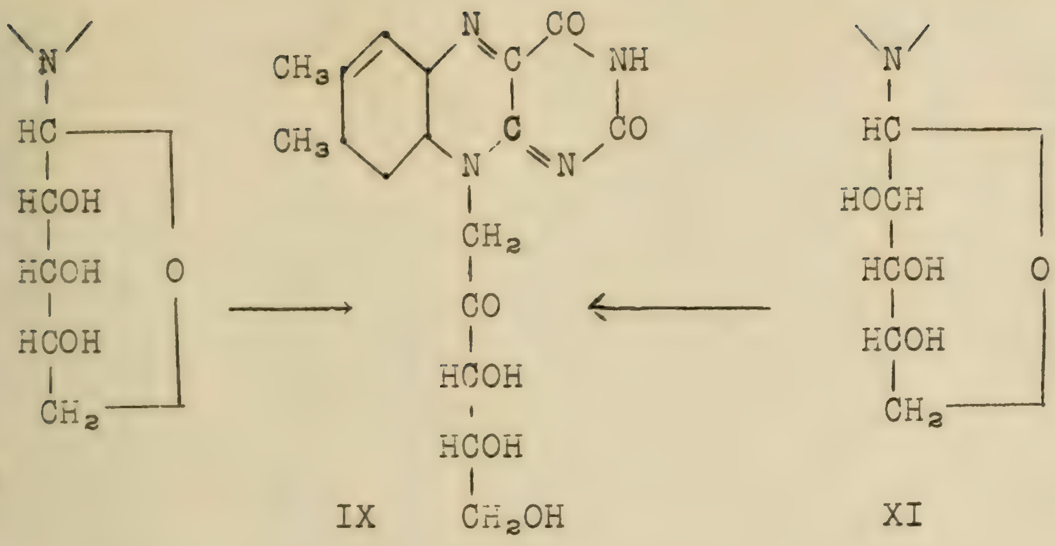


VI VII VIII

From this compound, lactoflavin can be synthesized by known methods (R = d-ribityl group, $-CH_2(CHOH)_3CH_2OH$):



Kuhn and Strobele have considered 6,7-dimethyl-9-d-ribosido-flavin (X) as an intermediate in the natural synthesis of lactoflavin, from which the lactoflavin is produced by reduction. It can now be assumed that the ribityl group undergoes an Amadori rearrangement, with subsequent reduction. The same isoglycosamine results from a N-d-arabinoside. It would be interesting to study the biological and chemical properties of 6,7-dimethyl-9-d-arabinosoflavin, to determine whether it acts as an intermediate in the biogenesis of lactoflavin.



X IX XI

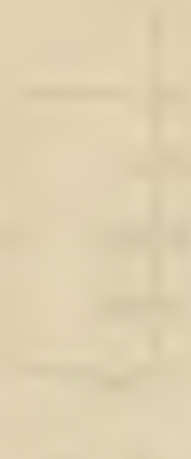
2. Hydrogenation of isoglycosamines

Mention was made above of the catalytic hydrogenation of a d-isoarabinosamine (VII) to a d-ribamine (VIII). Investigations on such hydrogenations grew out of an attempt to find a procedure for quantitatively measuring iso-sugar-amines. Hydrogenation of N-aryl-iso-sugar-amines in acid solution results in hydrogenation of the benzene nucleus, but in weakly alkaline solution, reduction takes place only in the side-chain. Obviously two possible epimers are possible, but the hydrogenation has proved to be stereo-selective for the most part. As the table below shows, only one isoglycosamine, l-isoarabinosamine, has been found to give both epimeric hydrogenation products.

Isoglycosamine	Hydrogenation product
p-Tolyl-d-iso-glucosamine	p-Tolyl-d-mannamine
p-Tolyl-l-iso-rhamnosamine	p-Tolyl-l-rhamnamine
p-Tolyl-d-iso-galactosamine	p-Tolyl-d-galactamine
p-Tolyl-d-iso-xylosamine	p-Tolyl-d-lyxamine
3,4-Dimethylphenyl-l-iso-arabinosamine	3,4-Dimethylphenyl-l-ribamine or -l-arabinamine
3,4-Dimethylphenyl-d-iso-arabinosamine	3,4-Dimethylphenyl-d-ribamine

Depending on conditions of hydrogenation, the l-ribamine or l-arabinamine can be obtained from the l-iso-arabinosamine.

The configuration of carbon 2 can be determined by the use of a simple rotation rule.



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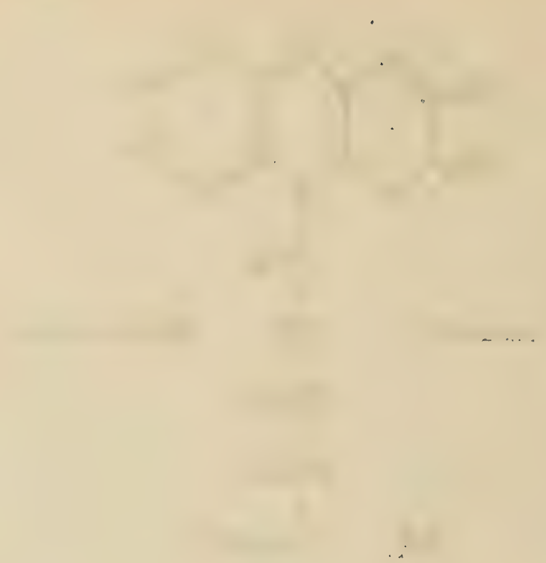

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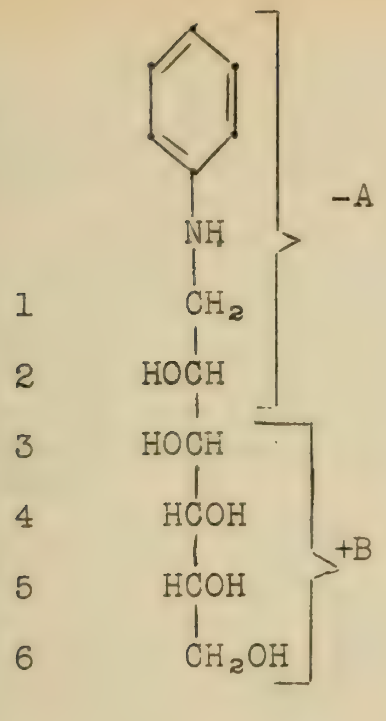
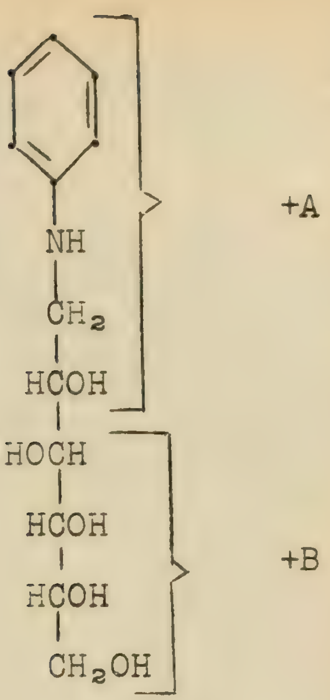
XII



XIII



Molecular rotations: +9500 -5700

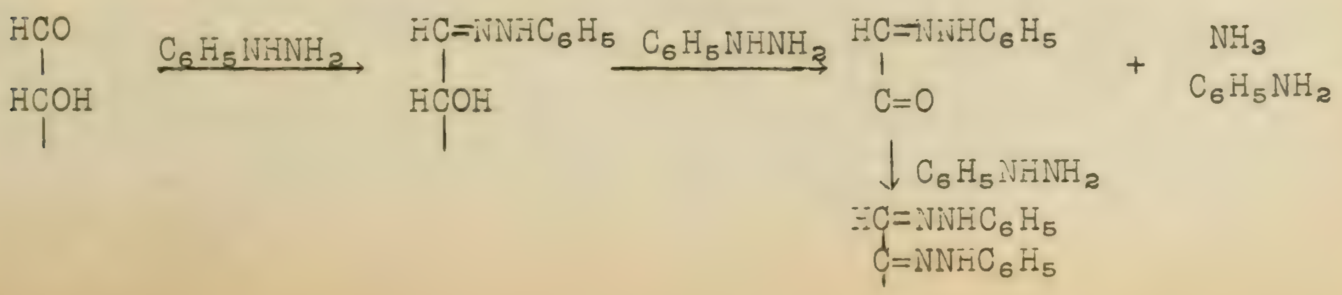
If the -OH group is projected on the right, as in phenyl-d-glucamine (XIII), the rotation is negative, or toward the left. This holds true for the N-aryl derivatives and the flavins. The rotatory power of the carbon 2 can be seen if the rotation of sections A and B of the molecule are measured. Rotation of A is positive if the -OH group on carbon 2 is on the right; rotation of B is positive if the -OH group on carbon 5 is on the right. Therefore, in the phenyl-d-mannamine (XII) and phenyl-d-glucamine (XIII):

$$\begin{array}{rcl} -A + B & = & +9500 \\ +A + B & = & -5700 \\ \hline +A & = & -7600 \\ +B & = & +1900 \end{array}$$

Part A of the molecule, containing one asymmetric center on carbon 2, has four time the rotatory power of part B, which includes the rest of the asymmetric centers.

3. Theory of osazone formation

In osazone formation, out of the three molecules of phenylhydrazine which enter into the reaction, one is converted into aniline and ammonia; the mechanism has therefore beenprojected as follows:



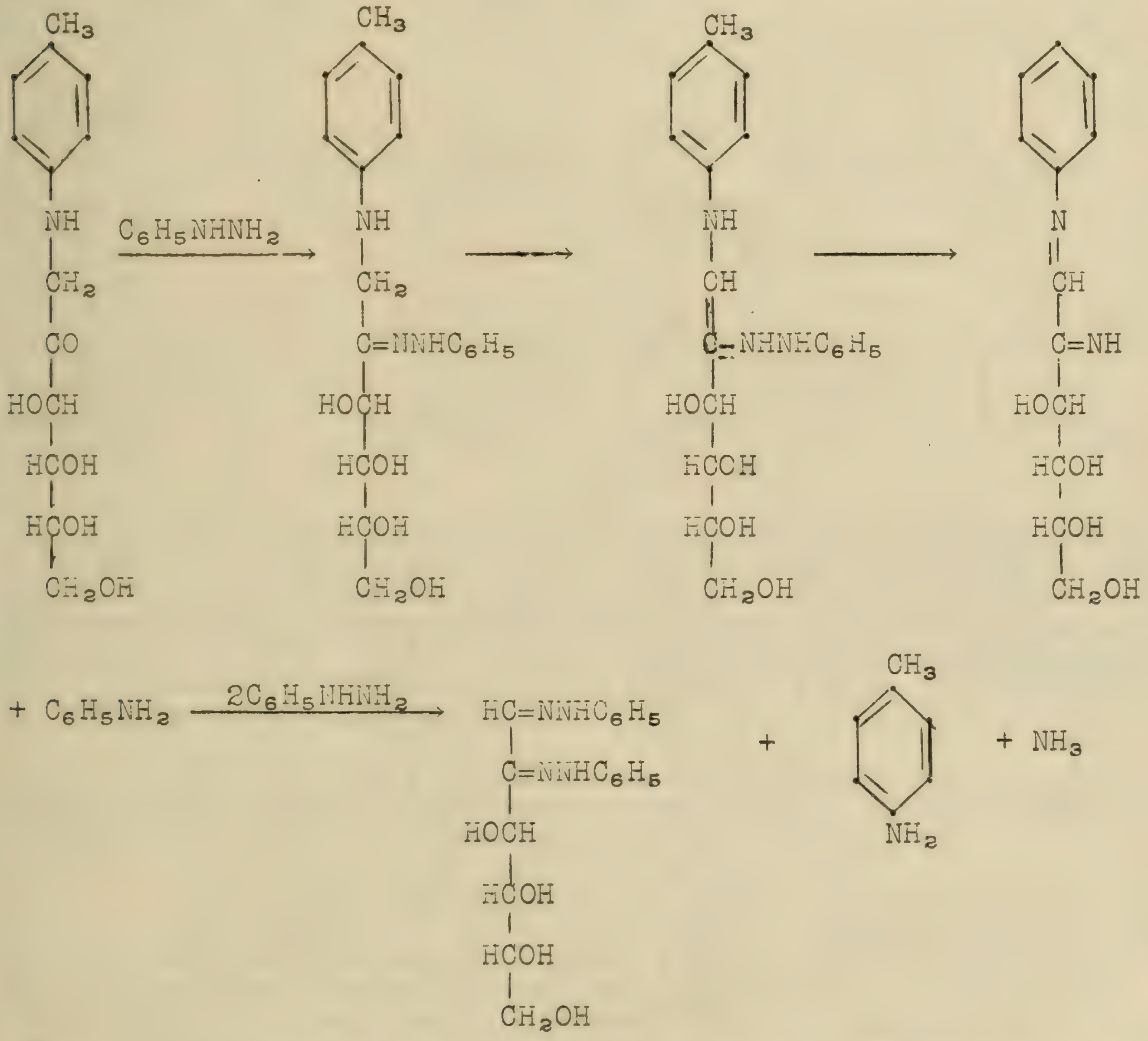
$$\begin{array}{l} \text{HCO} \\ | \\ \text{HCOH} \\ | \end{array} \xrightarrow{C_6H_5NHNH_2} \begin{array}{l} \text{HC=NNHC}_6\text{H}_5 \\ | \\ \text{HCOH} \\ | \end{array} \xrightarrow{C_6H_5NHNH_2} \begin{array}{l} \text{HC=NNHC}_6\text{H}_5 \\ | \\ \text{C=O} \end{array} + \begin{array}{l} NH_3 \\ C_6H_5NH_2 \end{array}$$

$$\downarrow C_6H_5NHNH_2$$

$$\begin{array}{l} \text{HC=NNHC}_6\text{H}_5 \\ | \\ \text{C=NNHC}_6\text{H}_5 \\ | \end{array}$$

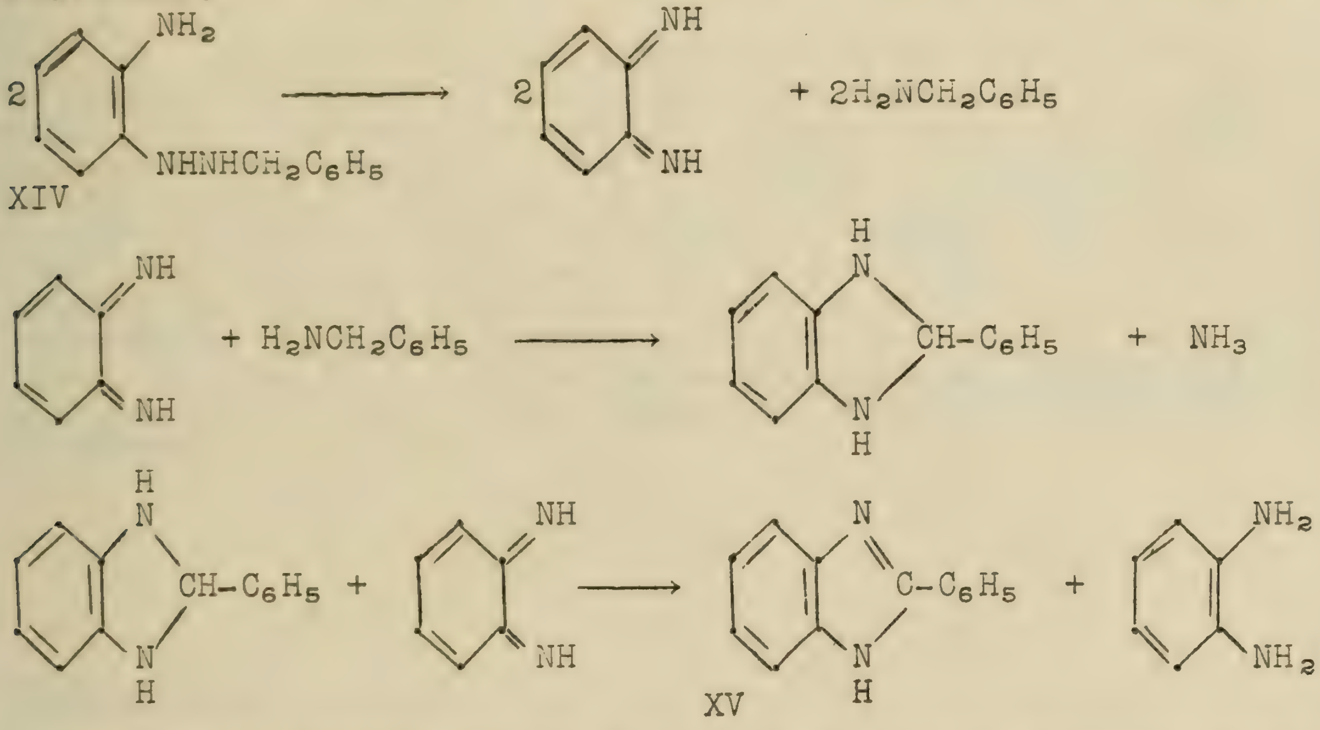
But it is strange that phenylhydrazine, a strong reducing agent itself, which is not affected by as strongly reductive a reagent as titanium trichloride, should be reduced by the -CHOH- group of carbon 2 of the sugar.

Reaction of phenylhydrazine with a sugar in acetic acid solution gives a 40-60 per cent yield of the phenylosazone, but the use of an aryl-isoglycosamine under similar conditions gives a nearly quantitative yield of the phenylosazone. In this latter reaction, the aryl amine of the isoglycosamine is split off in the osazone formation. On the basis of this, then, the mechanism for the formation of a phenylosazone from an aryl-isoglycosamine has been formulated as follows:



(1) A simple phenylhydrazone is first formed by reaction of phenylhydrazine with the carbonyl group. (2) A prototopic change then produces a di-amino-ethylene derivative, which in acid solution easily undergoes an intramolecular oxidation-reduction; in this case, the -NHNH- linkage is reduced. (3) The resulting imino-anil of glucosone reacts with two molecules of phenylhydrazine to give the phenylosazone.

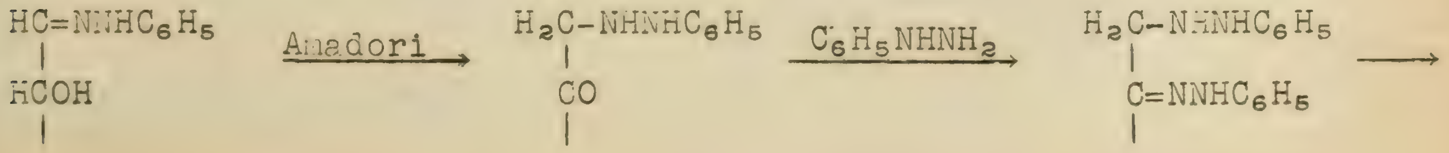
(1) Since an isoglucosamine forms an oxime, indicating a ketonic nature, the formation of a phenylhydrazone in the first step is reasonable. (2) The internal oxidation-reduction is based on the observed instability of di-amino-ethylene derivatives in acid solution. Franzen and von Furst found that *o*-amino-β-benzyl-phenylhydrazine (XIV), when warmed in acid solution, decomposed to aniline, ammonia, *o*-phenylenediamine, and phenylbenzimidazole (XV). Weygand finds this only reasonably explained by the following reactions:



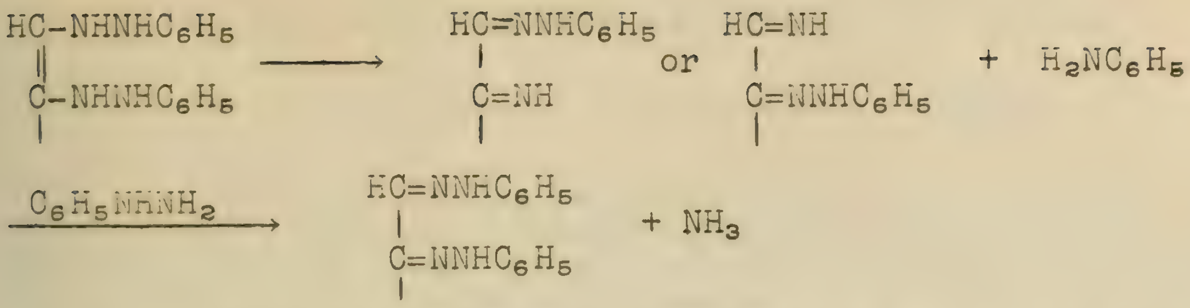
An intramolecular oxidation-reduction produces *o*-quinone-diimine and benzyl amine, which react to form phenyldihydrozenzimidazole, and this is in turn dehydrogenated by another molecule of quinone-diimine, giving phenylbenzimidazole and *o*-phenylenediamine. Similar decomposition takes place with *p*-amino-phenylhydrazine, but the *m*-compound is quite stable, presumably due to the impossibility of forming a *m*-quinone-diimine.

(3) The final exchange reaction takes place readily, since it is known that variously substituted phenylhydrazines will exchange with the groups on osazones already formed.

In the osazone formation of free sugars, it can be assumed that the hydrazone first formed undergoes an Amadori rearrangement, and the newly formed carbonyl group reacts with another mole of phenylhydrazine. From here the same intramolecular oxidation-reduction takes place as in the case of the phenylhydrazone of an isoglycosamine, and the -NHNH- group on either carbon 1 or 2 is reduced. An exchange of amino radicals gives the final phenylosazone.



$$\begin{array}{l} HC{=}NNHC_6H_5 \\ \;| \\ HCOH \\ \;| \end{array} \xrightarrow{\text{Amadori}} \begin{array}{l} H_2C{-}NHNHC_6H_5 \\ \quad | \\ \quad CO \\ \quad | \end{array} \xrightarrow{C_6H_5NHNH_2} \begin{array}{l} H_2C{-}NHNHC_6H_5 \\ \quad | \\ \quad C{=}NNHC_6H_5 \\ \quad | \end{array} \longrightarrow$$



$$\begin{array}{l} HC-NHNHC_6H_5 \\ \| \\ C-NHNHC_6H_5 \\ | \end{array} \longrightarrow \begin{array}{l} HC=NNHC_6H_5 \\ | \\ C=NH \\ | \end{array} \text{ or } \begin{array}{l} HC=NH \\ | \\ C=NNHC_6H_5 \\ | \end{array} + H_2NC_6H_5$$

$$\xrightarrow{C_6H_5NHNH_2} \begin{array}{l} HC=NNHC_6H_5 \\ | \\ C=NNHC_6H_5 \\ | \end{array} + NH_3$$

Arguments for the mechanism are the facts that (1) yields in osazone formation of free sugars are, under the best conditions, about equal to that by the Amadori rearrangement, which, therefore, appears as the limiting factor in yields; (2) glucose-phenylhydrazone on standing in dilute acetic acid at room temperature is converted to glucose-phenylosazone, but mannose-phenylhydrazone under like conditions remains unchanged. But it is a fact that N-mannosides undergo the Amadori rearrangement with much more difficulty than N-glucosides; (3) glucose-phenylhydroazone is known in more than two forms, meaning that besides the α- and β-forms, another keto form may exist, i.e., the 1-phenylhydrazine compound derived from the fructose.

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Reported by R. H. Hasek
March 19, 1941

SULFURYL CHLORIDE
AS A CHLORINATING AND SULFONATING REAGENT

Kharasch - University of Chicago

Although SO_2Cl_2 has been known for some time, its use in chlorinations and sulfonations has not been widespread. Kharasch indicates that this may be due to the fact that the chemical character of SO_2Cl_2 has been misinterpreted, since formerly it was used as a source of Cl_2 and SO_2. In the presence of peroxides Kharasch has shown that SO_2Cl_2 may easily be used as a source of the $Cl\cdot$ and $\cdot SO_2Cl$ free radicals. By careful adherence to certain experimental details, interesting synthetic reactions may be accomplished with the $Cl\cdot$ and $\cdot SO_2Cl$ free radicals. Furthermore, certain theoretical aspects concerning the properties of free radicals are brought to light by a consideration of SO_2Cl_2.

Chlorination

Since there are many known methods of chlorination, we are primarily interested in those cases where the use of SO_2Cl_2 is unique and necessary.

In Kharasch's method the compound to be chlorinated is refluxed with SO_2Cl_2 containing a small amount of benzoyl peroxide. Evolution of SO_2 and HCl begins immediately and the reaction is complete when no more gases are evolved.

$$RH + SO_2Cl_2 \xrightarrow[\text{peroxide}]{\triangle} RCl + SO_2\uparrow + HCl\uparrow$$

TABLE I

Conclusions to be drawn from Table I

1. Chlorination of side chains in aromatic hydrocarbons gives α chloro derivatives. This reaction is particularly useful when trying to chlorinate the side chain of a compound containing a reactive benzene nucleus, such as meta xylene. Other methods of chlorination lead to impure products due to nuclear substitution. If the nucleus is very reactive such as in fluorene and β methyl naphthalene, nuclear substitution is obtained even with SO_2Cl_2.

2. Secondary hydrogen atoms are chlorinated more easily than primary.

3. Presence of chlorine substituent increases the difficulty of further substitutions.

4. In the chlorination of acids, β and γ positions are more active than α.

Mechanism for the Chlorination Reaction

Step	Proof
1. $\phi CO{-}O{-}O{-}OC\phi \rightarrow 2\phi\cdot + 2CO_2$	known reaction
2. $\phi\cdot + SO_2Cl_2 \rightarrow \phi Cl + \cdot SO_2Cl$	initiates reaction
3. $\cdot SO_2Cl \rightarrow SO_2\uparrow + Cl\cdot$	no sulfonation products obtained, $\cdot SO_2Cl$ must decompose

4. $Cl\cdot + RH \rightarrow R\cdot + HCl$
5. $R\cdot + SO_2Cl_2 \rightarrow RCl + \cdot SO_2Cl$

Alternative Mechanism for last two steps

4'. $Cl\cdot + RH \rightarrow RCl + H\cdot$
5'. $H\cdot + SO_2Cl_2 \rightarrow HCl\uparrow + \cdot SO_2Cl$

Proof discussed later

Sulfonations

SO_2Cl_2 should, under the proper conditions, be a sulfonating as well as a chlorinating agent. However, no sulfonation products are isolated from the peroxide catalyzed reaction. This is strange in view of the fact that the mechanism of chlorination involves a $\cdot SO_2Cl$ free radical.

Sulfonation proceeds by an entirely different free radical mechanism, the presence of light and the absence of peroxides is essential. In all sulfonations, chlorination as well as sulfonation takes place. The most effective catalyst for sulfonations is pyridine, under whose influence the extent of chlorination is greatly reduced and good yields of the sulfonated product are obtained.

TABLE II

Mechanism of the Photochemical Sulfonation

It is obvious that a satisfactory mechanism for the photochemical sulfonation must explain plausibly why the use of peroxides either in the dark or in the light yields only chlorinated derivatives; while the use of light in the absence of peroxides and in the presence of pyridine yields both the sulfonated and chlorinated derivatives.

Step	Evidence
1. $SO_2Cl_2 \underset{}{\overset{\text{pyridine}}{\rightleftharpoons}} SO_2 + Cl_2$	Green color of Cl_2 appears in reaction
2. $Cl_2 \xrightarrow{h\nu} 2Cl\cdot$	known step
3. $Cl\cdot + RH \rightarrow R\cdot + HCl\uparrow$	discussed later
4. $R\cdot + SO_2 \rightarrow RSO_2\cdot$	
5. $RSO_2\cdot + Cl_2 \rightarrow RSO_2Cl + Cl\cdot$	

The organic radical formed in step (3) may undergo in solution the following changes:

(a) $R\cdot + SO_2Cl_2 \rightarrow RCl + \cdot SO_2Cl$

(b) $R\cdot + Cl_2 \rightarrow RCl + \cdot Cl$

(c) $R\cdot + SO_2 \rightarrow RSO_2\cdot$

Of these three possibilities reaction (c) should require the least energy of activation, since no bond is broken, and this reaction should be most favored. It must be postulated that the $RSO_2\cdot$ free radical cannot react with SO_2Cl_2 at any appreciable rate, since in the peroxide-catalyzed reaction, in which both substances must be present, no measurable quantity of sulfonated products is formed.

It is the presence of free chlorine in the reaction mixture which directs the course of the reaction toward the formation of the alkyl sulfonyl chloride.

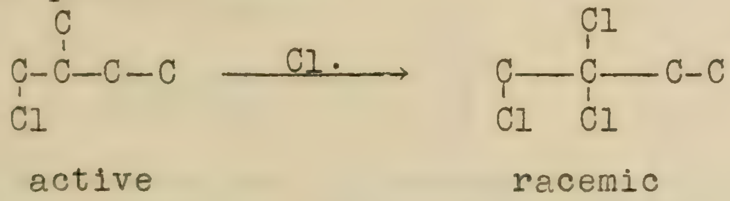
Free Radical Mechanisms

Because of insufficient knowledge concerning the properties of free radicals, it is usually difficult to describe the mechanism of a free radical reaction. Kharasch's last papers in this series deal with an attempt to decide whether the following reaction proceeds by mechanism (1) or (2).

(1) $RH + Cl\cdot \rightarrow RCl + H\cdot \xrightarrow{Cl\cdot} RCl + HCl\uparrow$

(2) $RH + Cl\cdot \rightarrow R\cdot + HCl \xrightarrow{Cl\cdot} RCl + HCl\uparrow$

In the case of active amyl chloride, Kharasch obtained a racemic chlorinated product.



The fact that the substitution of a chlorine atom for a hydrogen atom results in an inactive product was interpreted as support for the hypothesis that the reaction involves an alkyl free radical. Mechanism (1) would have yielded an active product accompanied by a Walden inversion.

Mechanism (2) is therefore correct.

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Reported by Henry Yuska
March 26, 1941

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2. [illegible]
3. [illegible]

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TABLE I

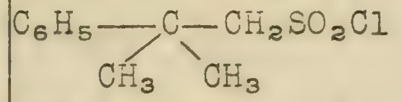
CHLORINATIONS

Type of Compound	Name	Yield expected chlorinated deriv.	Other Products
aliphatic	cyclohexane	72% monochloro derivative	28% dichloro deriv.
	n-propyl chloride	50% 1,2-dichloro 30% 1,3-dichloro	
	n-butyl chloride	15% 1,2-dichloro 40% 1,3-dichloro 15% 1,4-dichloro	
aromatic	toluene	80% benzyl chloride	
	toluene (excess SO_2Cl_2)	benzal chloride, 80%	
	ethyl benzene	α-chloro ethyl benzene, 85%	
	tertiary butyl benzene	β-chloro *tert*. butyl benzene, 70%	
	meta xylene	80% meta xylyl chloride	
	o-nitrotoluene	zero	
	fluorene		nuclear substitution.
	β-methyl naphthalene		nuclear substitution.
Acids and Acid chlorides	propionic acid	50% β-chloro-acid	40% α-chloro acid
	n-butyric acid	45% γ and β-chloro acids (mixture)	35% α-chloro acid
	Acetic Acid	poor yield	
	trimethyl acetic acid	good yield monochloro deriv.	
	$ChCl_3$ CCl_4 ϕCl CH_2Cl	No reaction. May be used as solvents	

TABLE II

SULFONATIONS

(strong light used, peroxides absent)

Compound	Catalyst	% Chlorinated product	% Sulfonated Product
cyclohexane	pyridine	9%	$C_6H_{11}CH_2SO_2Cl$ 55%
ethylbenzene	pyridine	75%	$C_6H_5CH_2CH_2SO_2Cl$ 12%
tertiary butyl benzene	none	22%	 $C_6H_5-\underset{CH_3\quad CH_3}{C}-CH_2SO_2Cl$ 39%
propionic acid	none	20% α-chloro acid	60% β-sulfo acid
_n_-butyric acid	none	8% chloro acid	55% mixture β and γ sulfo acids
lauric acid	pyridine		60% β, and other sulfo acids.

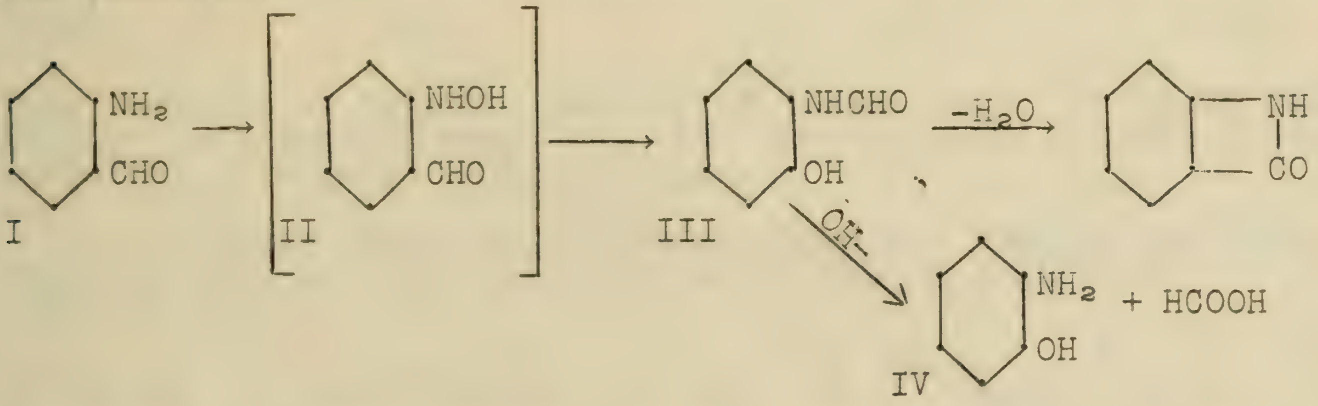
In no case has the α-sulfo acid been shown to be formed.

The chloro acids formed simultaneously were largely the α-chloro acids.

CONVERSION OF ORTHO- AND PARA-SUBSTITUTED AROMATIC ALDEHYDES TO THE PHENOLS BY MEANS OF PEROXIDES

A. von Wacek, et al   Universitat Wien

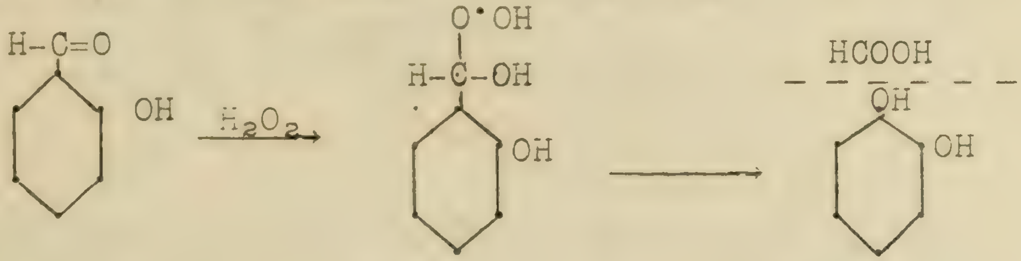
In 1903, Bamberger found that o-amino phenol and formic acid were obtained when o-amino benzaldehyde was treated with Caro's acid. As intermediate he found "isohydroxylaminobenzaldehyde" $C_7H_7NO_2$, found to be o-hydroxylaminobenzaldehyde (II) which could be dehydrated to anthranil, or would change to the amino phenol in the presence of a base. He postulated the following mechanism for the reaction:



This involves the formation of the hydroxyl amine (II), the o-formamino phenol (III), with a saponification to the o-amino phenol (IV). It was known at that time that phenyl hydroxylamine would undergo a change to the phenol, and also that amines on oxidation may yield hydroxylamines.

About six years later, Dakin observed that aromatic aldehydes and ketones with an -OH group in the ortho- or para-position could be oxidized, in alkaline solution, to the polyhydric phenols. Bromine or chlorine atoms and nitro groups in the 3,5-positions do not interfere with the reaction, but iodine compounds of this type and also the meta substituted hydroxy compounds are oxidized to the acid. Na_2O_2, BaO_2, perbenzoic acid and Caro's acid will produce the change to the phenol, while other oxidizing agents give the acid.

A possible mechanism for this reaction involves the formation of an aldehyde-peroxide, followed by a cleavage, in the case of salicyladehyde to catechol and formic acid.



According to this, all hydroxy aldehydes, whether ortho- or para-, or meta should give the diphenol. Aldehyde-peroxides, on the other hand, usually go to the acid.

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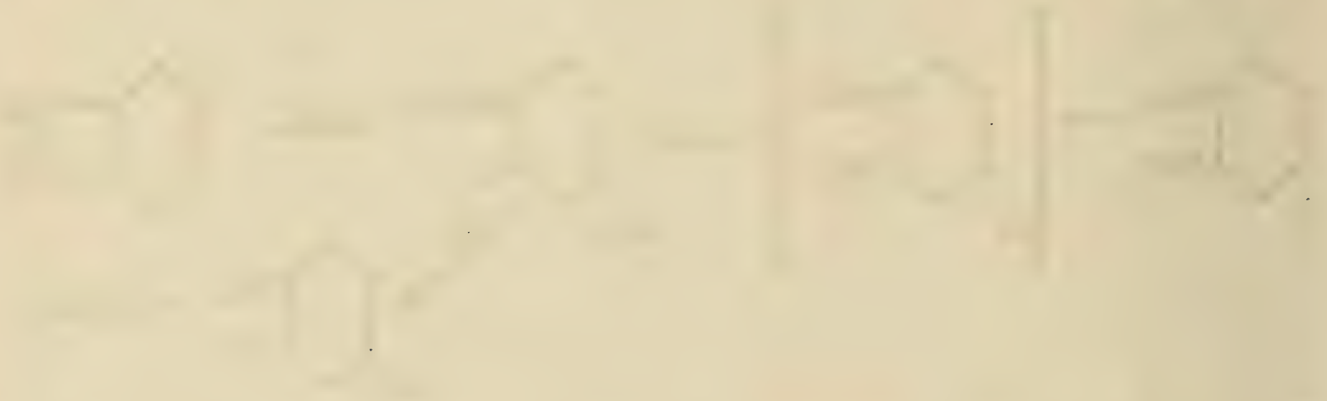

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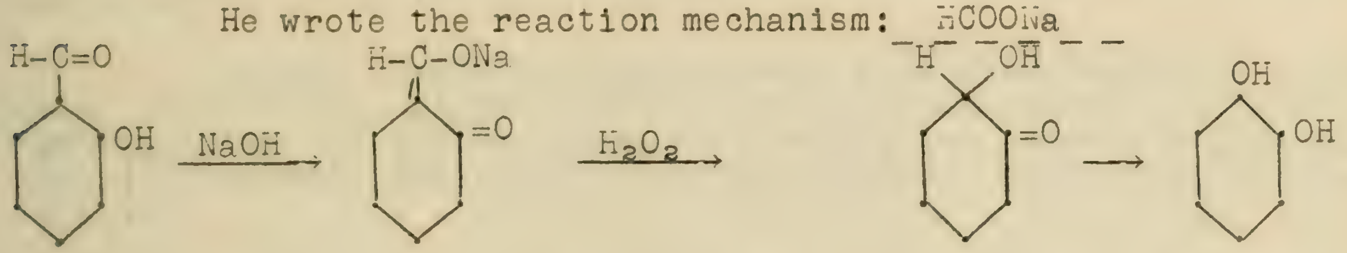
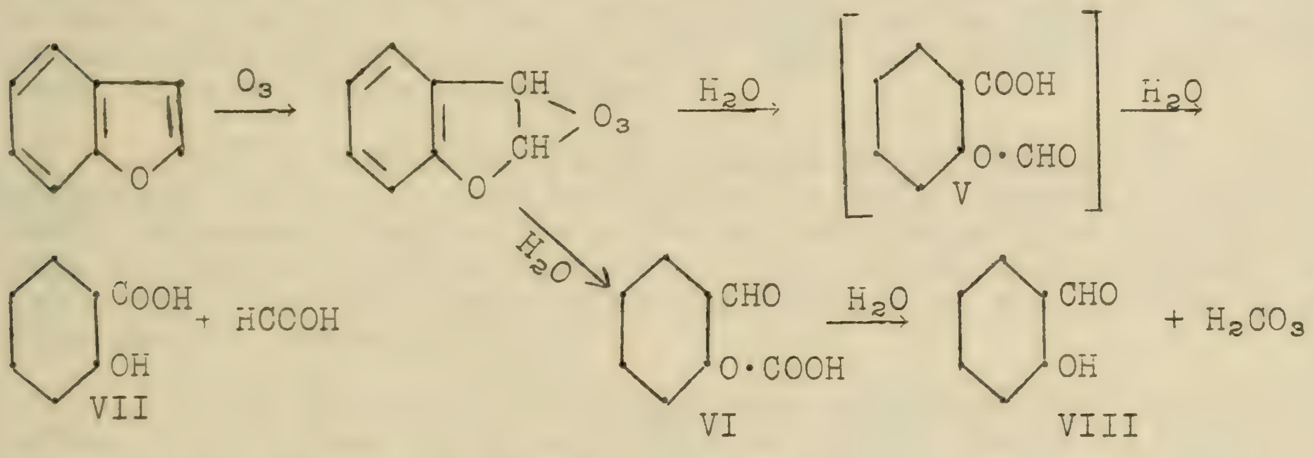
Dakin used the theory of a quinoid structure, postulated by Hantszch to account for the color of some of these compounds, to explain his three main observations: (1) alkali, with attendant salt formation, is necessary for the reaction; (2) meta derivatives which have no possible quinoid structure fail to give the phenol; (3) if the quinoid structure is blocked by making an ether of the -OH group; the conversion to the phenol does not take place.

He wrote the reaction mechanism:

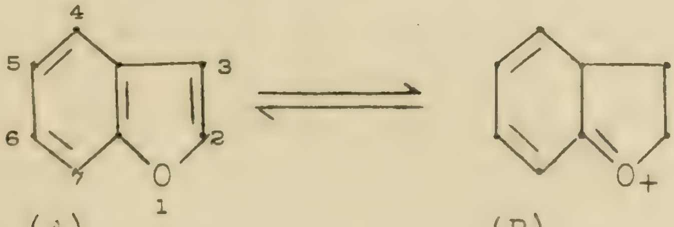


This does not explain the failure of 3,5-di-iodo-4-OH benzaldehyde to give the expected reaction. The theory of the quinoid intermediate is disproved by later work.

Wacek, Eppinger and Bezard recently studied the effect of ozone on cumarone and benzothiophene. They postulated:



Salicylic acid, salicylaldehyde, the formic and carbonic acids are accounted for by this series of reactions, but some catechol was also produced. This could be explained if mesomeric forms of cumarone exist, making possible a split between the benzene ring and the #3 carbon.



(A) (B)

Catechol could result from the reaction of ozone on (B). Contrary to this mechanism is the observation that diphenylene oxide, with a similar structure does not give catechol, while o-hydroxy styrene, which has no mesomeric forms, does.

More logical is the theory of a secondary reaction of the intermediate salicylaldehyde, since Dakin established that it would yield catechol in alkaline solution with H_2O_2. In this case, alkali is not necessary, and the decomposing ozonide performs the function of the alkaline H_2O_2. If oleic acid ozonide is decomposed by water in the presence of salicylaldehyde, catechol results, but in the absence of compounds which can form ozonides, ozone oxidizes the aldehyde group to the acid.

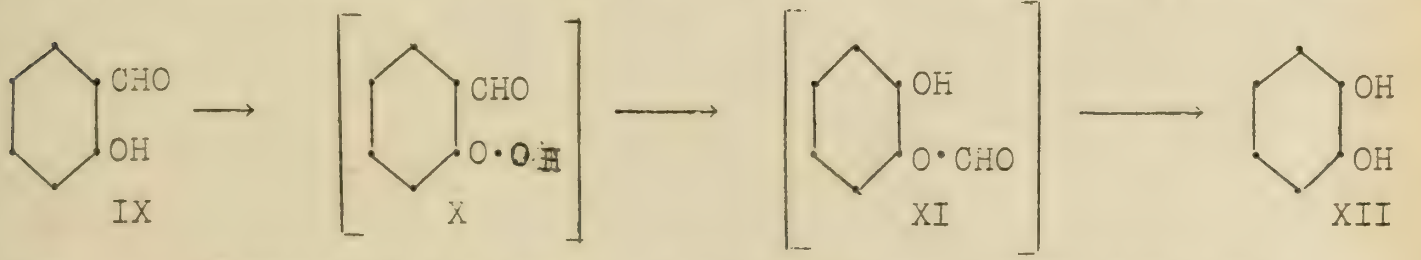
Methyl cumarones will undergo a similar reaction, giving ester derivatives of the phenol group as intermediates. Benzothiophene behaves exactly as cumarone, forming the corresponding thiophenol compounds, the products being isolated, of course, as the disulfides.

The most recent work by Wacek, et al, comfirms Dakin's work where salicylaldehyde in alkaline solution with H_2O_2 yields catechol. They effectively dispute the quinoid theory, however. The conversion occurs in varying H$^+$ concentrations, going quantitatively in glacial acetic acid and to some extent in pyridine, showing that salt formation is not necessary. Even the color change described by Dakin is shown to be atypical, since it is observed in an acetone solution of the aldehyde although no catechol is produced, while it is absent in cases where the reaction is brought about by a decomposing ozonide.

If a double bond will undergo an oxidative cleavage by peroxides, it should also be cleaved by other reagents, such as $KMnO_4$ or ozone. Further, a -C=N- and -C=S should be broken in the same way as the -C=C-, which would give catechol in the case of *o*-amino and *o*-mercapto benzaldehydes, instead of the *o*-amino phenol and thiocatechol actually found.

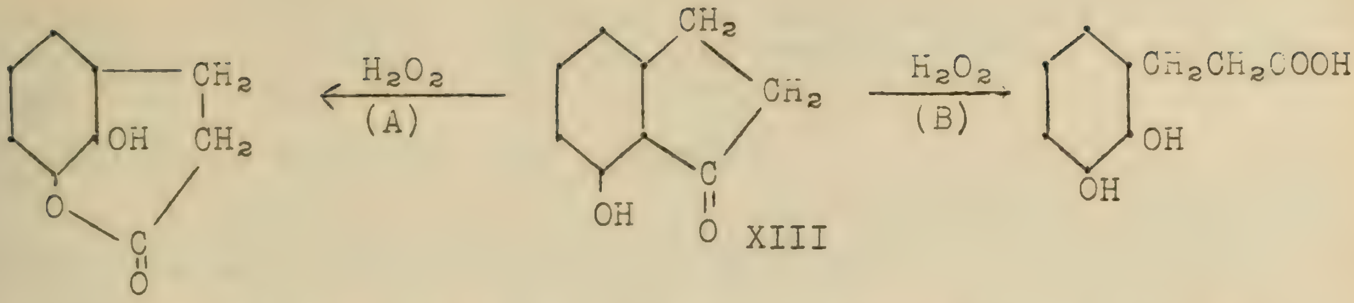
The conclusion of Dakin that compounds containing an ether rather than a free -OH group, will not yield phenol is verified, except in the case of the *o*-methoxybenzaldehyde, where 3-10% catechol is produced.

Wacek writes a mechanism for the salicylaldehyde reaction entirely analogous to that given by Bamberger for the *o*-amino phenol.



Compound XI was not isolated. Work on alcohol-peroxides and hydroxy phenyl ketones substantiates these rearrangements.

If the rearrangement is blocked, as in the case of *o*-hydroxy-α-hydrindone (XIII), no conversion to the phenol can take place.



XIII

Scheme (A) is the one which the rearrangement would have to follow, and this is impossible due to the ring structure. According to Dakin's theory, (B) is possible, with a breaking of the ring, and introduction of an -OH group. Since (B) actually does not occur, the rearrangement theory seems most plausible.

In conclusion, the following generalizations can be made: An aldehyde or ketone undergoing this type of reaction must have an hydroxyl, amino, or mercapto either ortho- or para-. An unstable phenol peroxide is formed, which under the conditions employed, rearranges to the diphenol. With other oxidizing agents, the aldehyde is converted to the acid. Therefore, no true oxidation occurs with H_2O_2, but rather a substitution and rearrangement.

The authors claim that the experimental results point to the rearrangement theory rather than the quinone theory as the correct one.

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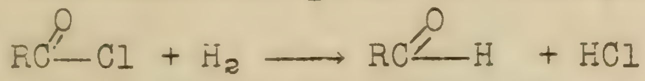
Reported by Elizabeth W. Maycock
March 26, 1941

The synthesis of an aldehyde is a problem commonly met in research. Recent work involving the development of new methods and more extensive study of the familiar reactions makes the consideration of this type of synthesis timely.

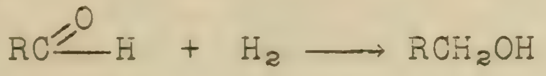
I. Method of Rosenmund and Zetzsche

Aldehydes are prepared by the replacement of the chlorine atom of an acid chloride group by hydrogen:



$$R\overset{O}{\overset{\|}{C}}-Cl + H_2 \longrightarrow R\overset{O}{\overset{\|}{C}}-H + HCl$$

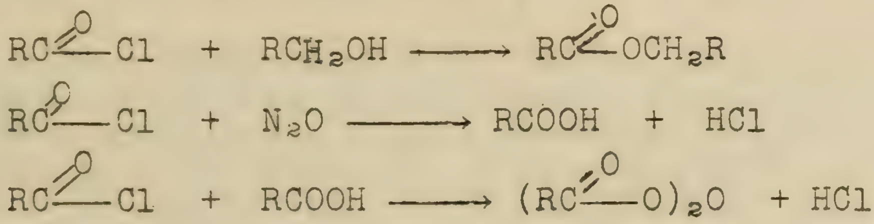
Catalytically activated hydrogen effects the replacement so that the aldehyde is exposed to further reduction:



$$R\overset{O}{\overset{\|}{C}}-H + H_2 \longrightarrow RCH_2OH$$

$$RCH_2OH + H_2 \longrightarrow RCH_3 + H_2O$$

The products can react with the starting material:



$$R\overset{O}{\overset{\|}{C}}-Cl + RCH_2OH \longrightarrow R\overset{O}{\overset{\|}{C}}-OCH_2R$$

$$R\overset{O}{\overset{\|}{C}}-Cl + N_2O \longrightarrow RCOOH + HCl$$

$$R\overset{O}{\overset{\|}{C}}-Cl + RCOOH \longrightarrow (R\overset{O}{\overset{\|}{C}}-O)_2O + HCl$$

The method is successful only when the reduction stops at the first stage and the reaction conditions are fixed with this object in mind. The determining factor seems to be the activity of the aldehyde formed. If it is very active, the catalyst, which is usually palladium deposited on barium sulfate, is "poisned" by a small amount of a sulfur-containing compound called a "regulator." Quinoline-S, thioquinanthrene, and phenylisothiocyanate are commonly used. The presence of reducible groups other than the aldehyde group also makes the use of a regulator advisable. The next most important condition is the temperature of the reaction, which must be carefully regulated to obtain the best yields.

The usual experimental procedure is to dissolve the pure acid chloride in xylene, toluene, or decalin, add catalyst and regulator, if necessary, and pass in purified hydrogen, meanwhile raising the temperature gradually to the optinum point, which is judged by the rapidity of evolution of HCl. The reduction is interrupted when the flow of HCl stops and the aldehyde is isolated, often as the bisulfite compound.

Only a few aliphatic aldehydes have been prepared by this method, but the success attained in the preparation of chaulmoogryl aldehyde encourages further work in this field. For the preparation of heterocyclic aldehydes the yields average 60 to 70% in the coumarin, pyridine, pyrazole, and trazole series, although the presence of two or three chlorine atoms on the pyridine nucleus is necessary for success in that series. The yield of aromatic aldehydes usually ranges from 70 to 90%. Dialdehydes in both the aliphatic and aromatic series are rarely made by Rosenmund's method. Succinyl chloride and phthalyl chloride yield butyrolactone and phthalide, respectively.

II. The Stephen Method

Aldehydes are made from nitriles by conversion to imide chlorides with hydrogen chloride and subsequent reduction to imine hydrochloride by means of stannous chloride. Hydrolysis of the aldimine complex salts gives the aldehydes. The following equations represent the reactions taking place:

$$\mathrm{RC{\equiv}N + HCl \rightarrow RCCL{=}NH}$$

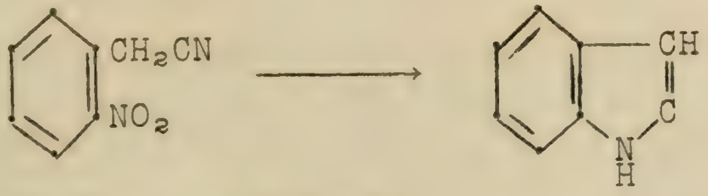
$$\mathrm{RCCl{=}NH + SnCl_2 + 2HCl \rightarrow RCN{=}NH{\cdot}HCl + SnCl_4}$$

$$\mathrm{RCH{=}NH + N_2O \rightarrow RCHO + NH_3}$$

The experimental procedure is to suspend anhydrous stannous chloride in dry ether and pass in dry hydrogen chloride, while stirring until the mixture separates into two layers. The flow of gas is then interrupted, the nitrile added, and the stirring continued for two hours by which time the crystalline aldimine hydrochloride stannic chloride complex [$(C_6H_5CH{=}NH{\cdot}HCl)_2SnCl_4$ in the case of benzaldehyde] has begun to separate. After precipitation is complete, the solid is removed by filtration and hydrolyzed with boiling water to the aldehyde.

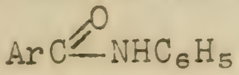
The method is applicable to the preparation of both aliphatic and aromatic aldehydes in excellent yields. There are a few limitations to the procedure. Steric hindrance militates against the production of o-tolualdehyde and α-naphthaldehyde by this method. Another exception to the generality of the reaction is the case of α-β-unsaturated aliphatic nitriles. With Δ'-cyclohexene nitrile and 6-methyl-Δ'-cyclohexene nitrile, the method fails and although cinnamaldehyde can be prepared in this way the yields in the series $Ar(CH{=}CH)_xCN$ fall off rapidly as x increases.

An interesting application of Stephen's method is the preparation of indole by the reduction of o-nitrophenylacetonitrile, both the nitro and the imide chloride groups being reduced when sufficient reducing agent is employed.



III. Method of Sonn and Muller

This method consists of three steps. First, an acid anilide is converted into an imide chloride by phosphorous pentachloride:



$$\mathrm{Ar}\overset{O}{\overset{\|}{C}}\mathrm{{-}NHC_6H_5 + PCl_5 \rightarrow ArCCl{=}NC_6H_5 + POCl_3 + HCl}$$

The chlorine of the imide chloride is replaced by hydrogen by means of stannous chloride in ether saturated with hydrogen chloride:

$$\mathrm{ArCCl{=}NC_6H_5 + SnCl_2 + 2HCl \rightarrow ArCH{=}NC_6H_5{\cdot}HCl + SnCl_4}$$

The anil (or Schiff's base), which is obtained as the tin complex compound, is hydrolyzed by dilute acid to the aldehyde and aniline:

$$\mathrm{ArCH{=}NC_6H_5 + H_2O \rightarrow ArCHO + C_6H_5NH_2}$$

The intermediates are not purified although they are usually isolated. The imide chlorides are made by mixing the anilide with phosphorus pentachloride in benzene, toluene, or tetrachloroethane and heating until solution takes place. The solvent and phosphorus oxychloride are evaporated under diminished pressure and the crude product is reduced exactly as in the Stephen method. The aldehyde is obtained by steam distilling the whole reaction mixture or isolating the complex salt, boiling with acid, and following this, steam distillation or extraction. The yields are about 85%.

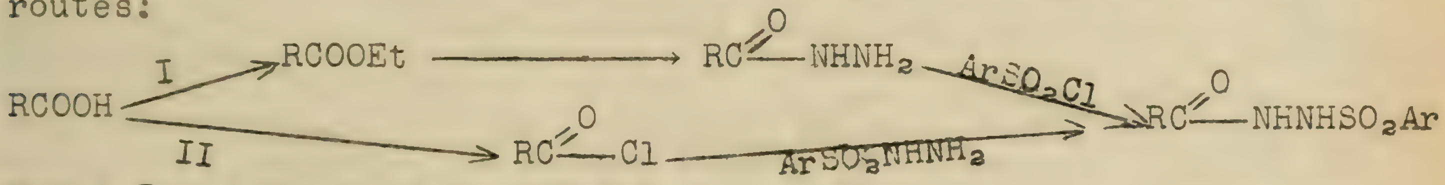
The method of Sonn and Muller is not applicable to the preparation of most aliphatic aldehydes because aliphatic imide chlorides are unstable. The decomposition probably starts with intramolecular migration of hydrogen:

$$>CH\text{-}Cl{=}NC_6H_5 \rightarrow >C{=}CCl\text{-}NHC_6H_5$$

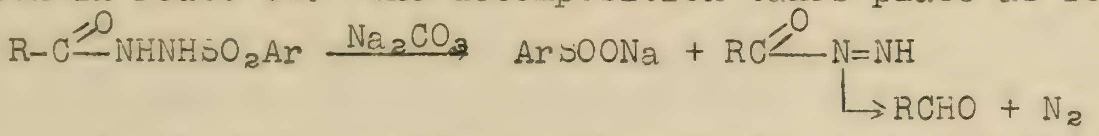
The presence of α-β unsaturation or the absence of hydrogen on the alpha carbon atom prohibits this migration and stabilizes the imide chloride. For the reduction of completely aliphatic unsaturated imide chlorides, stannous chloride must be replaced by a stronger reagent, chromous chloride.

IV. Method of McFayden and Stevens

Aldehydes are made from carboxylic acids by converting the acids to the arylsulfoneacylhydrazides and decomposing the latter with alkali. The sulfoneacylhydrazides are made by either of two routes:



Route I is the better method because of the tendency toward diacylation in route II. The decomposition takes place as follows:

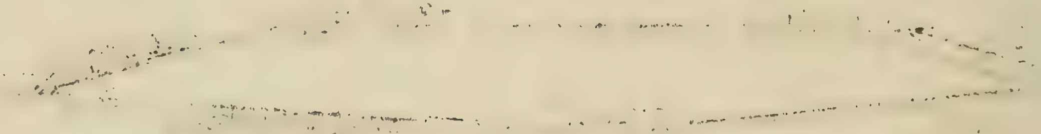


$$R\text{-}C(=O)\text{-}NHNHSO_2Ar \xrightarrow{Na_2CO_3} ArSOONa + RC(=O)\text{-}N{=}NH \rightarrow RCHO + N_2$$

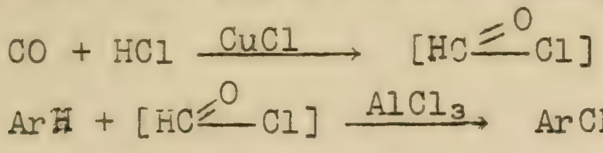
The acid hydrazides are obtained by heating 50% hydrazine hydrate and the ester in alcohol in an autoclave. The arylsulfonehydrazides are prepared by heating an aryl sulfonyl chloride with a pyridine solution of acid hydrazide and then pouring the mixture onto acid. The decomposition is carried out by mixing the sulfoneacylhydrazide with ethylene glycol and adding a large excess of sodium carbonate to the hot solution. The latter is cooled quickly when the reaction ceases and extracted with ether to give the aldehyde. In this way 4(4'methoxyphenoxy) benzaldehyde was prepared in 52% yield from the corresponding ester.

V. Gattermann's Methods

The formyl group may be regarded as an acyl group in which the radical is hydrogen. Therefore, just as acids and acid derivatives condense with various substances in the presence of certain anhydrous metal halides to give ketones, the formyl group is introduced by derivatives of formic acid. Thus Gattermann's methods are special cases of the Friedel-Crafts reaction.



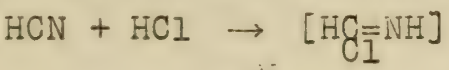
The Gattermann-Koch reaction employs carbon monoxide and hydrogen chloride, formyl chloride probably being formed as an intermediate. Aluminum chloride is used as the catalyst, but the reaction will not take place unless a small amount of cuprous halide is present.



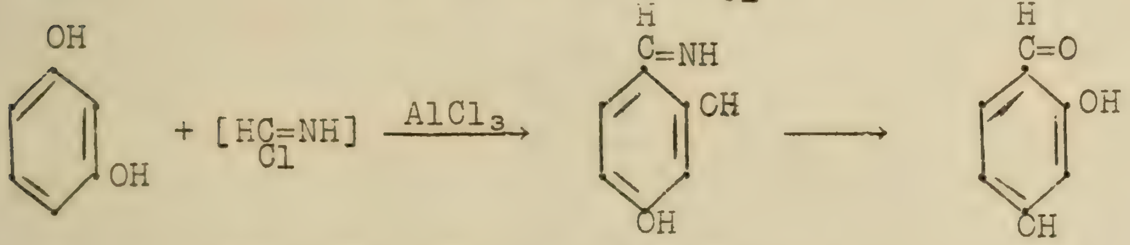
$$CO + HCl \xrightarrow{CuCl} [H\overset{\overset{O}{\|}}{C}-Cl]$$

$$ArH + [H\overset{\overset{O}{\|}}{C}-Cl] \xrightarrow{AlCl_3} ArCHO + HCl$$

When carbon monoxide is replaced by hydrogen cyanide, the formyl group is introduced by means of the hypothetical formimine chloride. The aldimine is produced and is hydrolyzed to the aldehyde. This is known as the Gattermann reaction.

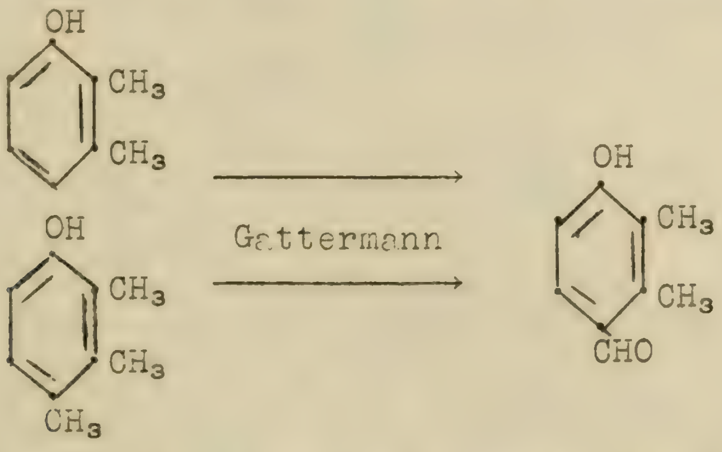


$$HCN + HCl \rightarrow [H\underset{Cl}{C}=NH]$$



Phenols and aromatic ethers react in this way at low temperature. More difficulty is experienced in substitutions with the alkylbenzenes. Higher temperatures and pressures lead to the desired result. Zinc chloride is often substituted for aluminum chloride, especially when sensitive compounds are involved. Adams has simplified the procedure by employing zinc cyanide, which reacts with hydrogen chloride to give the hydrogen cyanide, and zinc chloride necessary for the reaction. If the condensation requires $AlCl_3$, as in the case of phenol ethers, it is used in addition to $ZnCN_2$, the $ZnCl_2$ formed doing no harm. The yields in most cases of the Gattermann reaction range from 80% to quantitative.

The formyl group shows a strong tendency to enter the aromatic ring para to the hydroxyl or alkoxyl group.



Shah has discovered an apparent contradiction to this rule. The formyl group takes the position between the hydroxyl groups in some substituted resorcinols.

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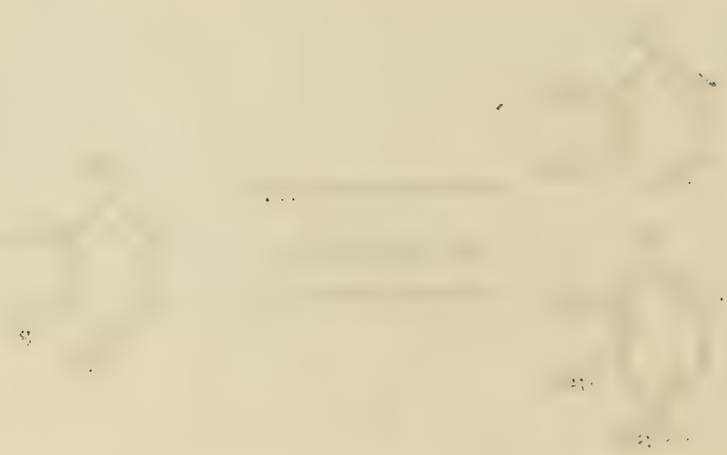

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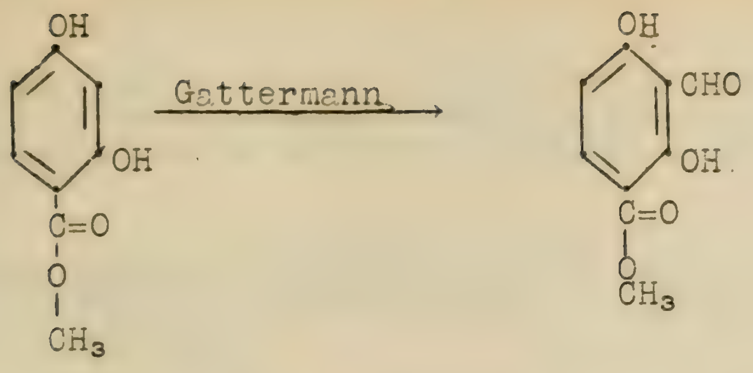
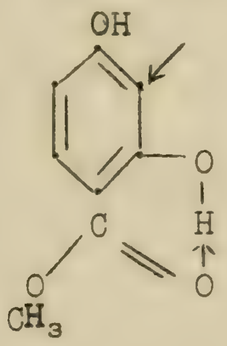


The explanation given is that chelation fixes the position of the double bonds in the benzene ring and the entering group attacks the point at the end of the double bond only.



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Reported by J. O. Corner
April 2, 1941

AROMATIC MERCURATION

Kobe and Doumani, University of Washington, Seattle, Washington

The general nature of the mercuration reaction and the increasing importance of aromatic mercury compounds in medicine and as useful intermediates in syntheses justify a consideration of this field.

Direct aromatic mercuration is a typical substitution reaction which generally proceeds easily to form mono-, di-, or polymercurated compounds.

$$ArH + Hg(OAc)_2 \longrightarrow ArHgOAc + HOAc$$

This represents the most general method of preparation of the mono-arylated mercuric compounds. The reaction may be applied to most of the important types of aromatic and heterocyclic compounds with the exception of aldehydes and some polyhydroxy phenols (catechol, hydroquinone) which are oxidized by the $Hg(OAc)_2$.

Generally, the reagent is $Hg(OAc)_2$ or $HgCl_2$ which may be used without a solvent, with glacial acetic acid or acetic anhydride, or with other solvents such as ethanol, nitrobenzene, or dichlorbenzene. The reaction temperatures range from "cold" to about 190°, and depending upon the reactivity of the compound more or less of the polymercurated compounds are formed. The difficulty encountered in the separation of the desired product is the outstanding disadvantage of this method.

Typical cases are summarized in the following table:

Compound	Reagents	Temperature	Time (hours)	%Yield of ArHgX
Benzene	$Hg(OAc)_2$, HOAc	90-100	2-9	92
Mesitylene	$Hg(OAc)_2$, HOAc, MeOH	Reflux	120	30
Durene	$Hg(OAc)_2$, HOAc, MeOH	Reflux	120	60
Aniline	$Hg(OAc)_2$, H_2O	20	3	82
o-Toluidine	$Hg(OAc)_2$, MeOH	20	48	15
Phenol	$Hg(OAc)_2$	100	1/4	97
o-Cresol	HgO, H_2O, HOAc	20	48-72	71
Phthalic anhydride	$Hg(OAc)_2$, H_2O, NaOH	170	6-10	85
Naphthoic acid	$Hg(OAc)_2$, H_2O; NaOH HOAc	Reflux	48	64
Nitrobenzene	$Hg(OAc)_2$	150	3-5	78
p-Nitrotoluene	$Hg(OAc)_2$	140	13	32
Furane	$HgCl_2$, NaOAc, EtOH H_2O	20	48	48
Thiophene	$HgCl_2$, NaOAc, EtOH H_2O	20	144	57
Pyridine	$Hg(OAc)_2$, H_2O	155	2.5	49

By *indirect aromatic mercuration* a functional group is replaced usually by a chloromercuri group. In many cases this method is advantageous since it leads to one particular isomer. Aryl mercuric halides may be obtained from various diazonium salts in fair yields (about 40 per cent from toluidines, aminophenols, β-naphthylamine.)

$$\mathrm{ArN_2Cl \cdot HgCl_2 + 2Cu \xrightarrow[\text{acetone}]{\text{ethanol or}} ArHgCl + N_2 + 2CuCl}$$

This also serves as an important method for the preparation of symmetrical diaryl mercuric compounds.

$$\mathrm{ArN_2Cl \cdot HgCl_2 \xrightarrow{\text{Cu, acetone}} \xrightarrow{\text{Cu, } NH_4OH} Ar_2Hg + N_2 + Hg}$$

Mercuric chlorides of hydrocarbons, nitro compounds, and chloro compounds have been made in 40-80 per cent yields by heating the aryl sulfinic acids with aqueous alcoholic mercuric chloride.

$$\mathrm{ArSO_2H + HgCl_2 \xrightarrow{\text{ethanol}} ArHgCl + SO_2 + HCl}$$

By means of the Grignard reaction or the sodium amalgam method aryl halides are converted to unsymmetrical or symmetrical mercuric compounds.

$$\mathrm{ArMgX + HgX_2 \rightarrow ArHgX + MgX_2}$$

$$\mathrm{2ArMgX + HgX_2 \rightarrow Ar_2Hg + 2MgX_2}$$

$$\mathrm{ArBr + Na_2Hg \rightarrow Ar_2Hg + 2NaBr}$$

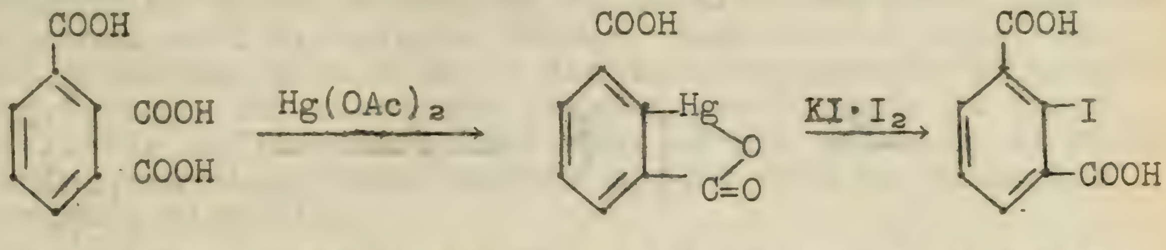
Since the yields from the amalgam method are comparatively low, use of this method has decreased.

The orienting effects of substituents appear to be modified in the mercuration reaction. The reaction proceeds normally when the substituent is *ortho*-*para* orienting, but a *meta* orienting group gives rise to all possible isomers with the *ortho*-isomer predominating. Both benzoic acid and nitrobenzene behave in this fashion, the percentages of products in the latter case being 52.6 *ortho*-, 38.5 *meta*-, and 8.9 *para*-mercuric derivatives.

The nature of the solvent and the temperature exert important effects in the direct mercuration reaction. In the case of phenol the percentage of the *ortho* isomer increases with the temperature. Excessively high temperatures promote polymercuration. The effect of solvent in the mercuration of phenol is evidenced by the formation of monomercurated (*ortho* and *para*) products in the absence of solvents but chiefly dimercurated compounds when water is used as the solvent.

The synthetic value of aromatic mercury compounds lies in the ease of replacement of the chloromercuri group and the reactivity of the symmetrical mercuric compounds. Aryl halides are obtained from the mercuric compounds by treatment with halogen

(usually bromine or iodine). Thus, p-iodobenzoic acid, o-iodophenol, and 8-halogen-1-naphthoic acids are easily prepared. The otherwise difficultly obtainable 2-bromo- and 2-iodo-3-nitrobenzoic acids and 2-halogenisophthalic acids are made from 3-nitrophthalic acid and hemimellitic acid, respectively.



The nitroso group is introduced by means of nitrosyl chloride. Providing oxidation can be avoided, nitro compounds can be made by the explosively violent action of nitric acid on the aryl mercuric halide.

Tetraaryl stannanes are obtained from aryl mercuric halides and Na-Sn alloys in good yields as compared to the low yields of the stannanes from the usual Grignard reaction. An important method for synthesis of halogenated arsines involves the chloromercuri compounds.

$$ArHgX + AsX_3 \rightarrow ArAsX_2 + HgX_2$$

$$2ArHgX + AsX_3 \rightarrow Ar_2AsX + 2HgX_2$$

Diaryl zinc compounds are best prepared from the mercury diaryls and zinc wool in xylene. Similarly, organic compounds of Li, Na, K, Mg, Cd, Al, Ga, P, As, Bi, and Se may be prepared.

$$3Ar_2Hg + 2SeBr_4 \rightarrow 2SeAr_2 + 3HgBr_2 + ArBr$$

Recent increased use of aromatic mercurials as antiseptics, germicides, fungicides, bacteriostatic agents, and disinfectants is evidenced in the patent literature. The method of manufacture of these compounds is usually that indicated below.

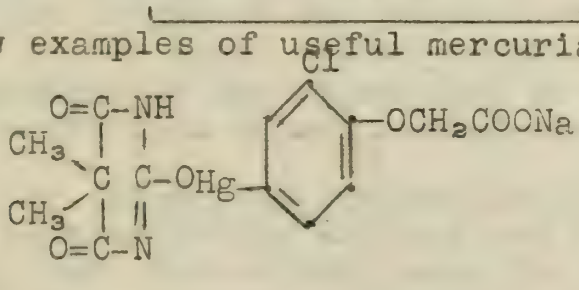
$$\begin{tikzcd} ArH \arrow[r] & ArHgOAc \arrow[r] \arrow[rr, bend right] & ArHgOH \arrow[r] & ArHgX \end{tikzcd}$$

A few examples of useful mercurials are shown.

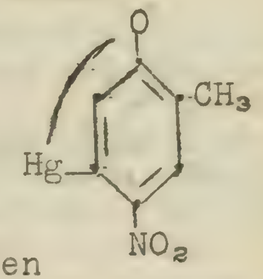
$C_6H_5HgNO_3$

C_6H_5HgOH

Merphenyl
(disinfectant)



Merbaphen
(diuretic)



Metaphen
(antiseptic)

These organic mercuric compounds are highly bacteriostatic and bactericidal and are less toxic and less irritating than the inorganic mercuric compounds.

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Reported by S.P. Rowland
April 2, 1941

ABSORPTION SPECTRA OF HYDROXY-ALDEHYDES, HYDROXY-KETONES, AND THEIR METHYL ETHERS

R. A. Morton - University of Liverpool

There are two kinds of absorption spectra. In the infra-red region absorption bands correspond to atomic absorption processes, Vibrations of atoms held by valence forces, such as C-H, O-H, and similar atomic groupings give rise to distinct absorption bands which seldom overlap. Since the vibration frequencies of many of these groupings are little influenced by the rest of the molecule in which they occur, infra-red absorption spectra may be used to determine molecular structure directly.

Absorption of visible and ultraviolet light is associated with a change in the electronic structure of part of the absorbing molecule accompanied by changes in atomic vibration and molecular rotation. These changes cause the broad nature of the absorption bands. Often more than one electronic absorption process can take place in a single molecule. Several broad absorption bands may be superposed partly or entirely. Thus, the visible or ultraviolet absorption spectrum of a compound is the resultant of all the various components making up a molecule and is, therefore, a physical property characteristic of the entire molecule. Consequently for many compounds absorption spectra serve as a convenient method of quantitative analysis, and for determining minute amounts of impurities. This is especially the case now that apparatus is available for making accurate quantitative absorption curves in both the visible and ultraviolet regions and doing it rapidly.

Absorption curves are plotted with the wavelength or frequency as abscissa, and log e as ordinate. The extinction coefficient, e, is calculated from spectrophotometer readings by the equation:

$$e = \frac{1}{L\ c} \log \frac{I_0}{I}$$

"I_0" is the intensity of the incident light;
"I" is the intensity of emitted light;
"L" is the length of the absorption cell;
and "c" is the molal concentration.

Thus "e" is independent of the dimensions of the apparatus, and does not vary with concentration unless association effects are present.

The use of absorption spectra in determining molecular constitution was inaugurated by Hartley and Dobbie in 1899. Since, absorption spectra have been widely used for this purpose. In 1925, using modern technique, Morton and Rogers repeated the work of Hartley and Dobbie; the determination of the structure of lactam and lactim isomerides which had "proved" the value of absorption spectra in determination of molecular structure. It was found that the structures of the lactim and lactam isomerides could not be determined from study of the quantitative absorption curves although their shapes were similar. Morton concluded that the shape of absorption curves was not important, and that, "Absorption spectra measurements should be interpreted by quantitative considerations concerning frequencies of maximum absorption."

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For two reasons conclusions based on absorption curves taken prior to about 1915 are to be doubted. Apparatus for quantitative measurement of absorption spectra was seldom available and the qualitative curves do not agree very well with those taken quantitatively. Also it was assumed that similar compounds would give absorption curves of similar shape and the structure of a compound was determined if it gave a curve similar to that of a derivative of known constitution. Morton and others have shown that this is not always true. Absorption curves presented in the literature from 1925 to the present seem in general to be accurate.

Interpretation of these curves is stilldifficult. Brode and Leermakers mention that attempts to resolve absorption spectra into additive and constitutive components have met with little success. However, "possibility of bringing out fine structure of the bands by making measurements at very low temperature offers hope of widening the scope of utility of the absorption spectrum method."

Morton states that relationships between widely different absorption spectra may be deduced if several premises are accepted. These are:

1. A very limited number of electronic absorption processes occur. They are essentially similar.

2. Intramolecular factors such as those arising from conjugation of double bonds, substitution in the benzene ring, and hydrogen bond formation, also intermolecular forces such as association and solvent-solute interactions result in discontinuous displacements of the wavelengths of maximum absorption, λ maximum.. Accordingly, the changes in energy required for a given electronic absorption process must be discontinuous.

3. The discontinuous energy displacements probably correspond to simple vibrational and rotational quanta.

4. Large displacements of λ maximum can occur without change in the basic electronic process.

5. It is assumed that λ maximum corresponds to the size of the quantum concerned in the electronic absorption process plus the energy of the most probable vibrational change. This, together with the assumption of discontinuous quantized displacements of λ maximum points to the possible existence of similar positions of maximum absorption for some of the compounds in a series containing the same chromophore.

Absorption spectra of hydroxy-aldehydes, hydroxy-ketones, and their methyl ethers were studied. These compounds all contain the phenyl chromophore and the carbonyl chromophore, which is discussed as a unit with the phenyl chromophore - the benzoyl chromophore. The site of the electronic process causing absorption is especially important as regards the effects of substituents introduced into a molecule on λ maximum. and the intensity of absorption. The site giving rise to each broad absorption band in these compounds was determined.

The phenyl chromophore. Benzene in hexane solution shows eight narrow bands between 2300-2700 A. (A = Angstrom units,) The maximum extinction coefficient, e, varies from 60 to 30. When an envelope is drawn about these curves the wavelength of maximum absorption is 2550 A, log e max. = 2.48. Benzene also possesses another absorption band farther in the ultraviolet, λ maximum is 1900 A, log e maximum = 4.0. Substitution increases the wavelength of maximum absorption and the intensity of absorption; usually it decreases the resolution of fine structure. Introduction of "transparent" groups such as alkyl or halogen radicals has little effect on benzenoid absorption:

Compound	λ max. A	log e max.
Benzene	2543*	2.48
Toluene	2620	2.48
Chlorobenzene	2640	2.51

* Alcoholic solutions were used, unless otherwise stated.

Other groups such as nitrile, carboxyl, hydroxyl, methoxyl, and amino have a greater effect.

Compound	λ max. A	log e max.
Benzonitrile	2700	2.90
	2250	4.10
Benzoic acid	2620	3.25
	2270	4.15
Phenol	2730	3.25
	2150	4.00
Anisole	2720	3.35
Aniline	2845	3.24
	2340	4.06

The long wave band of benzene is both displaced towards longer wavelengths and increased in intensity. Disubstitution of methyl groups and halogens increases λ maximum, the effect increasing in the order o,m,p. Disubstitution of hydroxyl, carboxyl, and amino groups again moves λ maximum in the direction of longer wavelengths, with the para compounds showing the greatest change. The introduction of the second substituent has less effect than the first. Introduction of two different substituents, each of which has a considerable effect when alone, gives values shown in the table below:

	ortho		meta		para	
Compound	λ max.A	log e	λ max.A	log e	λ max.A	log e
Hydroxy benzoic acid	3055	3.68	2990	3.48	2547	4.20
	2360	3.95	2330	3.96		
Amino benzoic acid	3375	3.67	3205	3.63	2890	4.30
	2470	3.83	2450	3.80	2180	3.90
	2180	4.40	2200	4.30		
Aminophenol	2860	3.60	2860	3.52	3015	3.43
	2330	3.68			2340	3.90

For the hydroxy and amino benzoic acids the displacement of the long wave benzenoid band towards longer wavelengths is greater in the ortho and meta compounds than in the para. The "para effect" is shown -- a large displacement of the short wave band towards longer wave lengths together with a slight displacement of the long wave band. This often results in superposition of the two bands with a consequent increase in intensity.

Phenyl and carbonyl chromophores combined. The spectra of acetophenone and of benzaldehyde in alcohol are almost identical and are representative of the general class:

λ max., A	3200	2870	2400	1990
log e max.	1.7	3.02	4.12	4.3

All these bands are considered as belonging to the benzoyl chromophore. The site of absorption must still be located. This may be done by comparison with the compounds.

Compound	λ max. A	log e max.
Mesityl oxide	3270	1.6
Acetone	1990	4.0
o-Hydroxybenzoic acid	2100	4.3 (short wave band)
Benzoic acid	2620	3.25
	2270	4.15
Phenol	2730	3.25
	2150	4.00
Aniline	2845	3.24
	2340	4.06

It is seen that the 2870 A and the 2400 A bands in the benzoyl chromophore correspond to the long and the short wave bands of the phenyl chromophore shifted by the effect of the carbonyl group, while the 3200 A and 1990 A absorption bands are caused by electronic transitions in the carbonyl group. These agree in intensity as well as in position.

In identification of sites of processes giving rise to absorption bands of hydroxy and methoxy aldehydes and ketones, benzaldehyde and salicylaldehyde are compared:

	λ max. A	log e	λ max. A	log e	λ max. A	log e
Benzaldehyde	3250	1.25	2790	3.25	2430	4.2
Salicylaldehyde	3250	3.48	2550	4.0		

At first glance it seems that the 3250 A band of salicylaldehyde corresponds to that of benzaldehyde and is due to carbonyl absorption. However, the spectra of ortho and meta hydroxy and methoxy benzaldehydes and ortho hydroxy and amino benzoic acids are to be compared with the spectrum given by salicylaldehyde:

For the hydroxy [illegible] oic acids [illegible]

[illegible] in the main [illegible]

shown [illegible] displacement of the first wave band for [illegible]

[illegible] together with slight [illegible]

This [illegible] in [illegible]

[illegible] in [illegible]

Phenyl [illegible]

[illegible] and are represented:

λ max. [illegible]

log ε max. [illegible]

All [illegible]

[illegible]

Compound	λ max.	log ε max.
[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible] inert ve band

[illegible]

[illegible] 11

[illegible]

[illegible] Benzaldehyde [illegible]

[illegible] aldehyde [illegible]

At first [illegible] A band [illegible] aldehyde [illegible]

[illegible]

C_6H_4 a	OMe	OH	OMe	OH	NH_2
	o	m	m	o	o
b	CHO	CHO	CHO	COOH	COOH
λ max. A	3195	3160	3145	3055	3375
log e max.	3.63	3.46	3.45	3.68	3.67

All these compounds give a band similar in intensity and in location to the 3250 A band in salicylaldehyde. The first three cannot undergo chelation, and the last two have no true carbonyl band in this region. It is apparent that the 3250 A band corresponds to the long wave benzenoid band in benzaldehyde displaced towards a longer wave length, and the 2550 A band to the 2430 A band in benzaldehyde. The carbonyl band at 3200 A is masked. Similarly the longest wavelength of maximum absorption in other hydroxy aldehydes, ketones, and their methyl ethers was found to correspond to an electronic process in the benzene nucleus.

The absorption spectra of some of this series of compounds in different solvents were measured. Groups of curves often exhibited surprisingly similar values of λ maximum. Working with the long wave benzenoid band, a constant frequency difference of 1450 cm^{-1} was observed between neighboring maxima. This frequency difference was used to calculate a series of wavelengths of maximum absorption, starting with λ maximum for a solution of salicylaldehyde in excess alkali, which exhibited the longest λ maximum.

Compound	Medium	Observed λ max. A	Calculated λ Max. A
Salicylaldehyde	Excess alkali	3785	3785
o-Hydroxyacetophenone	Excess alkali	3590	3588
m-Hydroxybenzaldehyde	Excess alkali	3590	3588
o-Hydroxyacetophenone	1 eq. alkali	3410	3411
Salicylaldehyde	Hexane	3430	3411
Salicylaldehyde	Ethanol	3250	3250
o-Hydroxyacetophenone	Ethanol	3270	3250
o-Hydroxyacetophenone	Water	3245	3250
o-Methoxybenzaldehyde	Hexane	3100	3104
m-Hydroxybenzaldehyde	Hexane	3080	3104
m-Methoxybenzaldehyde	Hexane	3090	3104
			2970
Benzaldehyde	Hexane	2830	2847
Phenol	Alcohol	2730	2735
			2631
Benzene	Alcohol	2543	2534

The same values for λ maximum recur in this series of benzene derivatives. Therefore the possibility that such values show a discrete series is worth study. The agreement between calculated and observed values of λ maximum is good, indicating a probability that the original premises of investigation were correct. The results of this one series investigated could be fortuitous, and more work is

needed to definitely prove or disprove that such series of absorption wavelengths exist. Morton makes the suggestion that if these results are significant, then the effect of substituents of a chromophore on electronic absorption processes is the induction effect. This would result in stabilization of valency electrons at energy levels differing by integral steps. The effect of substituents on the benzenoid absorption is in general to displace the spectrum as a whole in the direction of longer wavelengths, implying a changed initial energy state of the valence electrons such that a smaller quantum of energy can now effect essentially the same electronic transition.

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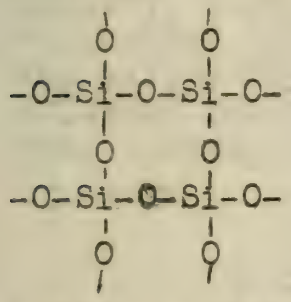
Reported by Vern McIntosh, Jr.
April 9, 1941

ORGANO-SILICON POLYMERS

Rochow, Gilliam, Liebhafsky and Winslow General Electric,
Schenectady, New York
Andrianov U.S.S.R.

Oxygen containing silicon compounds are characterized by highly rigid crystal structures, the best example of which is silica. X-ray data led G.N. Lewis to consider the SiO_2 crystal a "giant molecule" of the type illustrated. The formation of alkyl silicon oxides, wherein at least one of the four electron pairs of the silicon octet is connected to an organic radical, eliminates some of the less favorable properties of silica due to the intractibility of its highly rigid structure.



There are two general methods of preparation of these alkyl silicon oxide polymers. The first is the hydrolysis of the alkyl silicon polyhalide, and the second is the hydrolysis of alkyl polyethoxy silicon compounds. These generalized syntheses are as follows:

$$\mathrm{RMgX} + \mathrm{SiCl_4} \rightarrow \underset{\text{alkyl silicon trichloride}}{\mathrm{RSiCl_3}}$$

$$\mathrm{RSiCl_3} + \mathrm{R'MgX} \rightarrow \mathrm{RR'SiCl_2}$$

$$\mathrm{RMgX} + \mathrm{Si(OEt)_4} \rightarrow \underset{\text{alkyl triethoxy silicon}}{\mathrm{RSi(OEt)_3}}$$

On hydrolysis, these halides and esters yield silicols, hydroxy silicon compounds, which in turn lose water intermolecularly to produce polymeric silicons and siliconic acids, so named because of their empirical formulae.

$$\mathrm{R_2SiCl_2} \xrightarrow{H_2O} \underset{\text{alkyl silicanediol}}{\mathrm{R_2Si(OH)_2}} \xrightarrow{-H_2O} \underset{\text{alkyl silicone}}{\mathrm{(R_2SiO)_x}}$$

$$\mathrm{RSiCl_3} \xrightarrow{H_2O} \underset{\text{alkyl silicanetriol}}{\mathrm{RSi(OH)_3}} \xrightarrow{-H_2O} \underset{\text{alkyl siliconic acid}}{\mathrm{(RSiOOH)_x}}$$

Early work on this class of polymers was done by Friedel and Ladenburg about 1875 and was reviewed and reinterpreted by Kipping about 1915. Friedel had prepared diphenyl silicone and reported its analysis and properties. Kipping, doubting the existence of such compounds, synthesized benzylethyl silicone and obtained a substance with the proper analysis, but with an unexpectedly high boiling point. Moreover, it could not be reduced, it formed no characteristic derivatives, and it proved to be a trimer on a molecular weight determination. In addition to this trimer, he obtained several less soluble fractions of much higher molecular weight oils, probably linear polymers.

Kipping, repeating Ladenburg's work on the siliconic acids, prepared and hydrolyzed phenyl silicon trihalide under varying conditions of temperature and pH. Dilute aqueous ammonia at 0° gave an

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[illegible] U.S.A.F.

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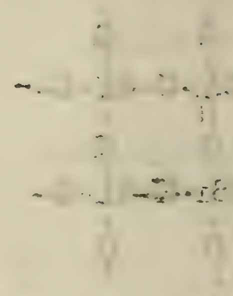


[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

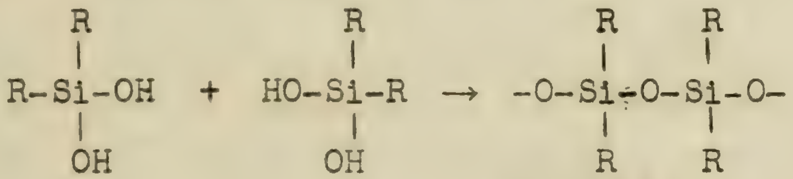
[illegible]

[illegible]

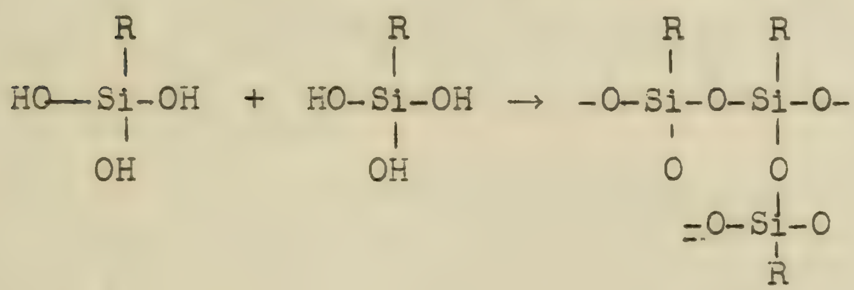
[illegible] linear polymers.

[illegible] temperature and pH. [illegible] ether soluble glue; water at room temperatures gave a white powder partially soluble in ether; and steam hydrolysis yielded a hard, solid mass quite insoluble in all solvents. Obviously, all hydrolysis products were polymers in different stages of condensation.

It remained for more recent workers to postulate the structures of these high molecular weight products. As a result of the publications of Andrianov in Russia and Rochow and Gilliam in this country, alkyl silicon oxide polymers have been characterized as "siloxane" types of compounds. That is, they contain Si-O-Si systems. The silicondiols are considered to condense linearly to give the silicone polymer, $(R_2SiO)_x$, while the triols yield the more highly crosslinked siliconic acids, $(RSiOOH)_x$

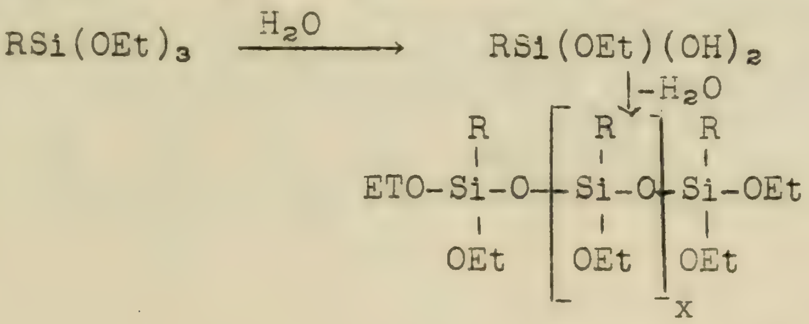


polysilicone



polysiliconic acid

Andrianov hydrolyzed alkyl triethoxy silicons with an amount of water insufficient to remove all three ester groups per molecule and obtained an alkyl polysiliconic ester.



R = C_2H_5, $C_4H_9(n)$

polysiliconic ester

In this country, Rochow and Gilliam, desiring to study an alkyl silicon oxide with a low alkyl to silicon ratio , accordingly prepared and hydrolyzed the methyl silicon chlorides. The di- and trichlorides are volatile liquids boiling between 65° and 70°, are extremely hygroscopic, and are explosive. Silicon tetrachloride was condensed with methyl magnesium bromide in ether solution and there was obtained the trihalide, the dihalide, or mixtures of the two depending upon the ratio of Grignard to silicon tetrachloride. The polymers were made by hydrolyzing the solution directly or by

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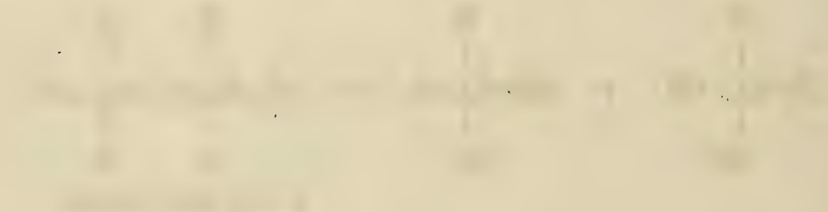

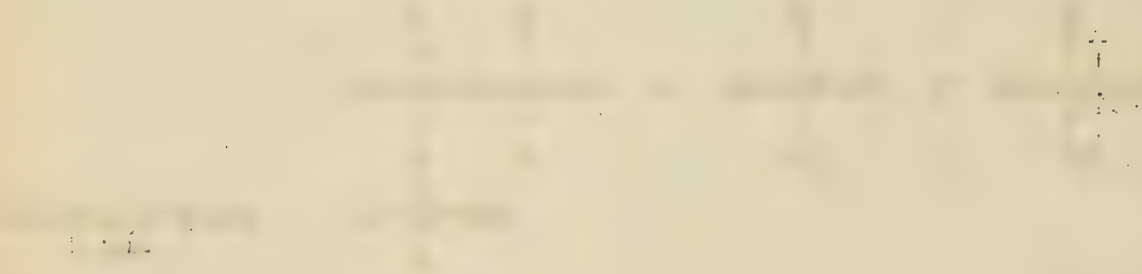

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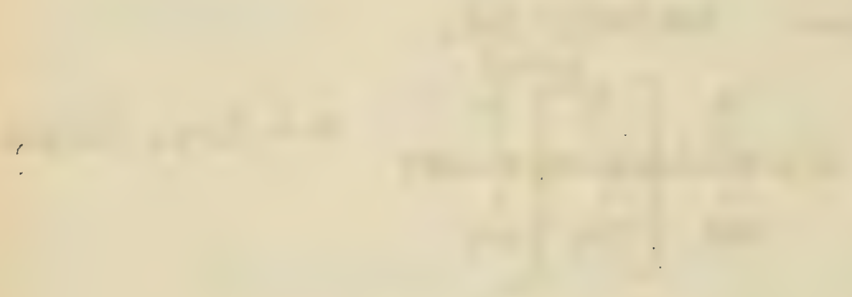

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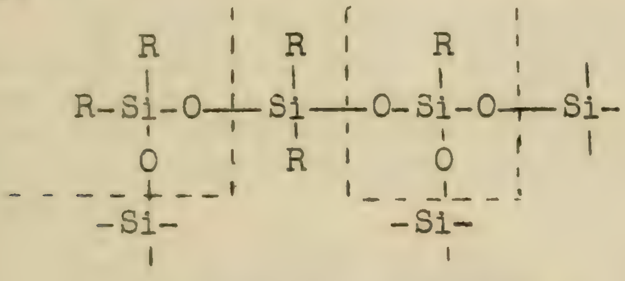
hydrolyzing a known mixture of the carefully purified halides. The siloxane resins so obtained may be considered as condensation copolymers of methyl silicondiol and methylsilicontriol. Residues of each are indicated within the dotted lines of the structural formula.



As the ratio of the methyl radical per silicon atom is increased, the initial condensation products become more volatile. These products could be stabilized by prolonged heating, all turning to hard horny resins. The middle range polymers, analyzing about 1.3 to 1.5 methyl groups per silicon atom, were found to be soluble in alcohols and hydrocarbons before gelation. Heat treatment rendered them infusible and insoluble. Remarkable thermal stability was exhibited by these resins. Heating at 550° *in vacuo* for sixteen hours and at 450° in hydrogen for one hour produced only a slight discoloration. One year's heating at 200° in air produced no change. At 300° in air, surface decomposition was slow, while at 400° in air, oxidation was fairly rapid.

As yet no uses for these polymers have appeared. Of course, the present preparation of the polyhalides and the polyethoxy compounds by a Grignard synthesis makes the cost fairly high. It has been indicated that glass manufacturers have contemplated the use of these resins as impregnants for glass-fiber products.

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Reported by J. C. Robinson
April 9, 1941

ALUMINUM ALCOHOLATES

Meerwein - Oppenauer

I. Meerwein's Reaction.

In 1925 Meerwein announced a new method for the reduction of aldehydes and ketones. The method consists in the reaction of aluminum ethylate with the aldehyde or ketone in absolute alcohol solution. In effect an interchange of functional groups takes place. Meerwein recognized that he was dealing with an equilibrium of the following type:

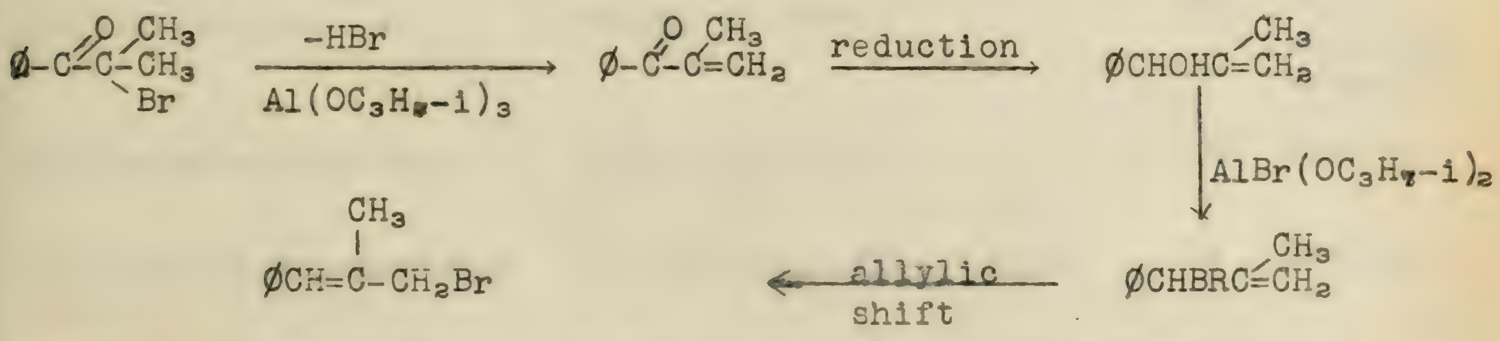
$$RCHO + \frac{Al}{3}OEt \rightleftharpoons RCH_2O\frac{Al}{3} + CH_3CHO$$

Other investigators have since found that use of aluminum isopropoxide is generally superior to use of aluminum ethylate. The reaction in this case is driven to completion by distilling out acetone as it is formed. Aluminum isopropoxide is easily made by refluxing aluminum turnings in isopropyl alcohol using a trace of $HgCl_2$ as catalyst.

Reduction with aluminum ethylate or isopropylate differs from ordinary methods in that it is specific for the carbonyl group. Nitro, unsaturated and halogenated carbonyl compounds have been successfully reduced to the corresponding nitro, unsaturated and halogenated alcohols. Some examples follow in Table I.

TABLE I (Page 2)

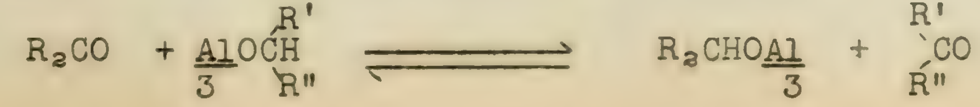
Reduction of α-halogen carbonyl compounds containing no hydrogen on the β-carbon atom takes place without loss of halogen, but if the compound contains β-hydrogen it is liable to lose halogen acid. For example α-bromopropiophenone yields only 30% of the bromohydrin, the rest of the yield being mainly alcohols that contain no bromine. α-Bromoisobutyrophenone yields about 37% of 2-methyl cinnamyl bromide instead of the expected α-bromoisobutyl phenyl carbinol. Stevens explains this by the following mechanism.



2-Bromochloestanone yields a product containing no bromine.

II. Oppenauer's reaction.

It can be seen from the equation



$$R_2CO + \frac{Al}{3}OCH\begin{matrix}R'\\R''\end{matrix} \rightleftharpoons R_2CHO\frac{Al}{3} + \begin{matrix}R'\\R''\end{matrix}CO$$

[illegible] — [illegible]

I. Meerwein's [illegible]

In 19[illegible] Meerwein [illegible] of aldehydes and [illegible]. [illegible] aluminum ethylate with the [illegible] solution. In effect [illegible] Meerwein recognized [illegible] following type:

RCHO + [illegible] → [illegible] + [illegible]

[illegible]

[illegible]

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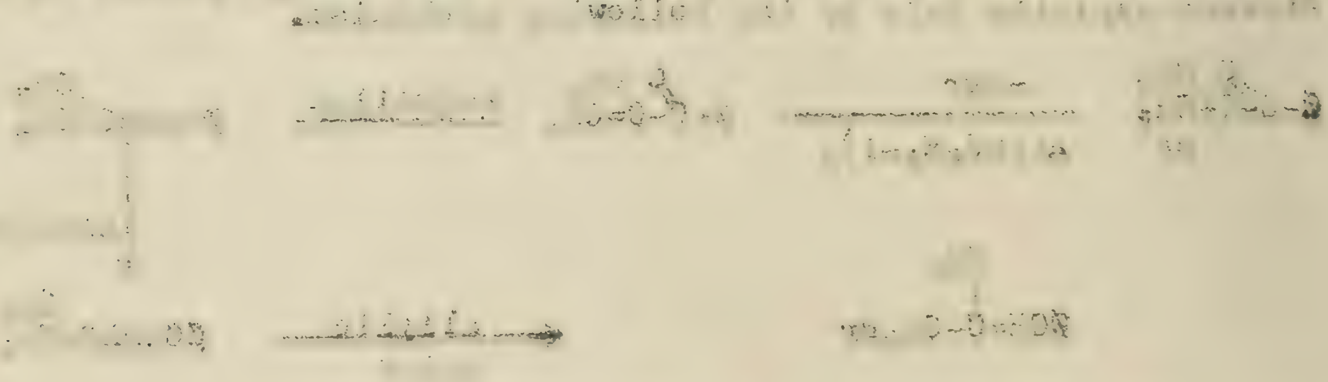
[illegible]



[illegible]

II. [illegible]'s [illegible]

[illegible] from the [illegible]

[illegible] → [illegible]

TABLE I

Carbonyl compound	Product	% Yield	Investigator
furfural	furfuryl alcohol	88	Meerwein
anisaldehyde	anisyl alcohol	80	Meerwein
p-nitrobenzaldehyde	*p*-nitrobenzyl alcohol	86	Meerwein
cinnamaldehyde	cinnamyl alcohol	86	Meerwein
benzoin	hydrobenzoin and isohydrobenzoin	96 (45/55)	Meerwein
β-bromcrotonaldehyde	β-bromcrotyl alcohol	good yield	Meerwein
p-nitrocinnamaldehyde	*p*-nitrocinnamyl alcohol	good yield	Meerwein
camphor	borneol and isoborneol	100	Lund
fluorenone	fluorenol	89	Lund
benzil	*meso*-hydrobenzoin	90	Lund
o-nitroacetophenone	methyl *o*-nitrophenylcarbinol	92	Lund
phenacyl bromide	bromomethyl phenyl carbinol	87	Lund
bromal	tribromoethyl alcohol	77	Lund
crotonaldehyde	crotyl alcohol	60	Young, Hartung Crossley
α-bromopropiophenone	1-phenyl-2-bromopropanol-1	30	Stevens
α-bromoisobutyrophenone	2-methylcinnamyl bromide	37	Stevens

that it should be possible to use the reaction to prepare carbonyl compounds from alcohols as well as alcohols from ketones. However no use was made of this property until 1937 when Oppenauer oxidized some high molecular weight alcohols to ketones by a modification of Meerwein's method for preparing alcohols.

To force the equilibrium to the right Oppenauer used a large excess of oxidizing ketone. For example, in the reaction

$$\text{cholesterol} + \text{acetone} \rightleftharpoons \text{isopropyl alcohol} + \text{cholestenone}$$

with 200 moles of acetone to one of cholesterol and a temperature of 64°, there was obtained a yield of 98% cholestenone in 5-9 hours.

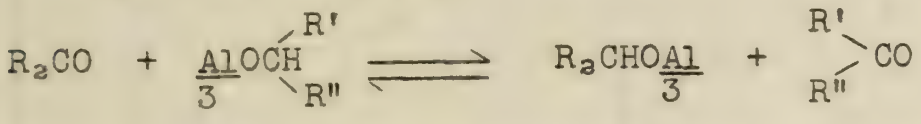
In his reactions Oppenauer employed aluminum t-butoxide as a carrier of aluminum to the alcohol to be dehydrogenated. In excess it also serves to diminish the retarding effect of moisture on the reaction. Tertiary butyl alcohol will itself, of course, not undergo oxidation without decomposition. It is prepared by the action of Al-Hg on anhydrous t-butyl alcohol containing a trace of $HgCl_2$ as catalyst, and is obtained as a white crystalline powder in yields of 60-65%.

For carrying out a typical oxidation the carbonyl compound is dissolved in hot acetone and benzene. (Benzene is required for solution of the aluminum t-butoxide.) Aluminum t-butoxide is added and the whole refluxed for a number of hours. The alcoholates are now decomposed with dilute sulfuric acid and the desired ketone obtained on evaporation of the benzene layer. In Table II are a number of oxidations that have been carried out.

TABLE II (page 4)

III. Equilibration of alcohols and carbonyl compounds by aluminum t-butoxide.

For the reaction



$$R_2CO + \frac{Al}{3}OCH\begin{smallmatrix}R'\\R''\end{smallmatrix} \rightleftharpoons R_2CHO\frac{Al}{3} + \begin{smallmatrix}R'\\R''\end{smallmatrix}CO$$

the position of equilibrium depends upon the oxidation-reduction potentials of the pairs,

R_2CO/R_2CHOH $\qquad$ $R'COR''/R'CHOHR''$

Adkins and Cox and Akins and Baker have determined the equilibrium concentrations for a number of such pairs of alcohols and ketones. From the equilibrium concentrations they have calculated relative reactivities (column 2, Table III) for the various ketones based on diisopropyl ketone as unity. Thus, according to Table III, if equimolecular amounts of cyclopentanone and cyclohexanol are allowed to react there would be at equilibrium 0.41 mole of cyclopentanone for each 0.09 mole of cyclohexanone. Obviously there is an enormous difference in oxidizing power among carbonyl compounds.

that it should be possible to use the reaction to [illegible] compounds from alcohols as well as directly from [illegible] to take advantage of this property [illegible] high-molecular weight alcohols [illegible] process for preparing [illegible].

To study the equilibria [illegible] a large range of [illegible]. The [illegible], in the reaction

[illegible]

with 200 [illegible] 60°, [illegible]

In [illegible]

The [illegible]

TABLE IV [illegible]

(1) Equilibrium of [illegible]

For the reaction

[illegible]

the constant of equilibrium depends upon [illegible]

[illegible]

[illegible]

TABLE II

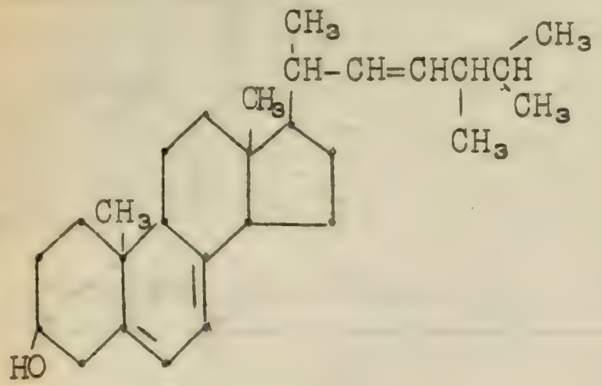
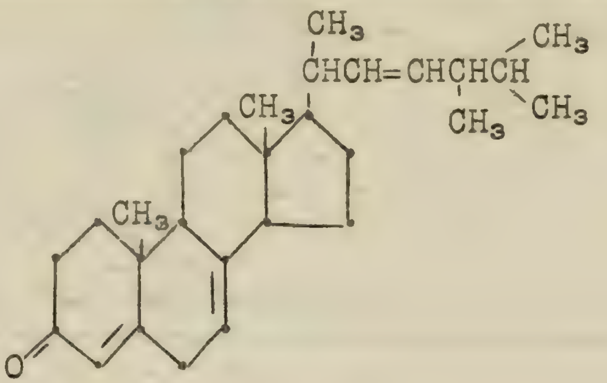
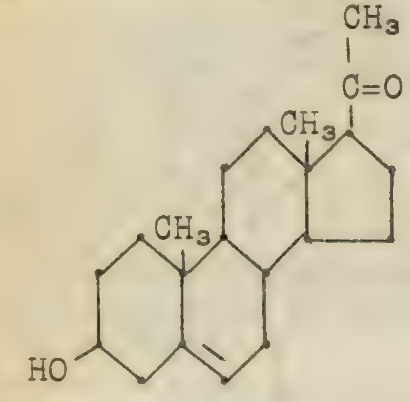
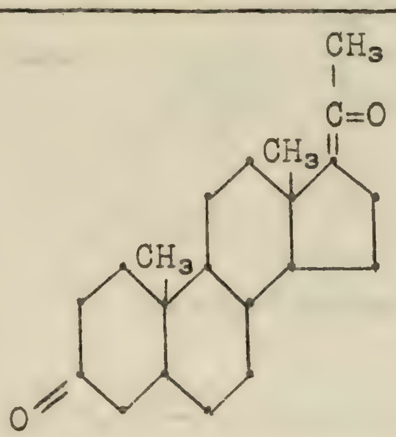
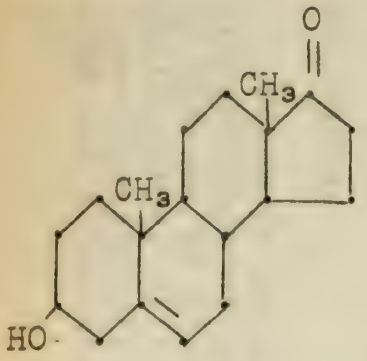
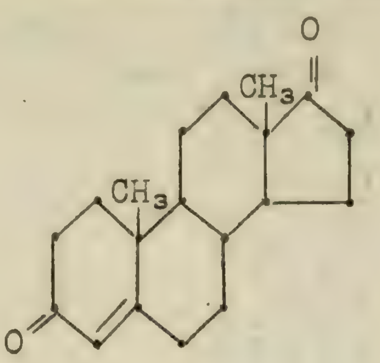
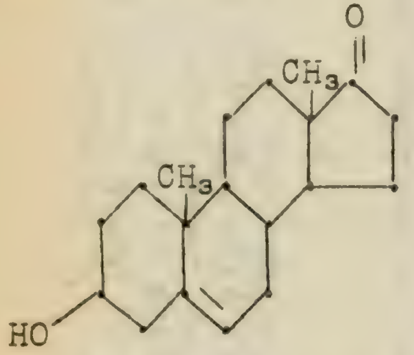
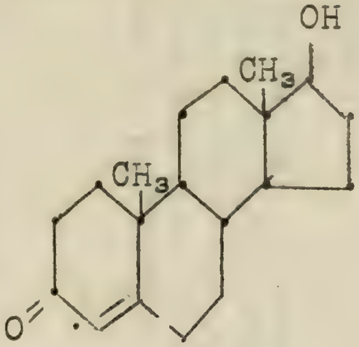
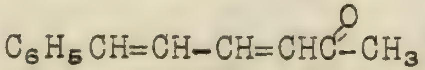
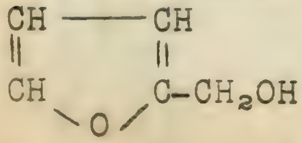
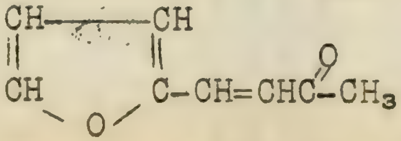
Alcohol	Product	% Yield	Reference
 ergosterol	 ergostatrienone	60	Oppenauer
 Δ^5-pregneolone	 progesterone	76	Oppenauer

TABLE II (Cont')

 △^{5}-dehydroandrosterone	 △ ^{4}-androstendione	87	Oppenauer
 △^{5}-dehydroandrosterone (boiling with Al t-butoxide, no acetone)	 testosterone		Oppenauer
$C_6H_5CH{=}CHCH_2OH$ cinnamyl alcohol	 $C_6H_5CH{=}CH{-}CH{=}CH\overset{O}{C}{-}CH_3$ Cinnamylidene acetone		Heilbron
 furfuryl alcohol	 furfurylidene acetone		Heilbron

In the third column of Table III are given the values in volts of the oxidation potentials of the carbonyl compounds with reference to the normal hydrogen electrode. These were calculated from the single oxidation potential of 9, 10-anthraquinone at the hydrogen electrode and the relative reactivities of the ketones. Thus E_0 for 9,10-anthraquinone is 0.154 volt. The value of E_0 for any other ketone is

$$E'_0 = 0.0296 \log K + 1.54$$

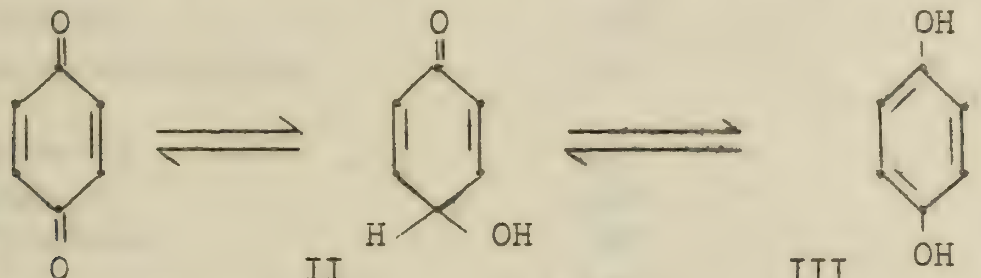
For cyclohexanone K $(0.45/0.09)^2$. Hence for cyclohexanone

$$E_0 = 0.0296 \text{ Log}(0.45/0.09)^2 + 1.54 = 0.159 \text{ volt}$$

From a consideration of the relative reactivities or oxidation potentials one can choose a good oxidizing agent for a specific alcohol and conversely can choose a good reducing alcohol for a specific ketone. It can be seen that acetone is only a fair oxidizing agent and that a large excess would actually usually be needed in Oppenauer's reaction to get a good yield of oxidation product.

An interesting point that may be noted is the great diversity in structure among ketones which have similar oxidation potentials. Anthroquinone, xanthone, acetone, and benzophenone, differing greatly in structure, have oxidation potentials in the same range. Unsaturation apparently makes little difference as does also fusion of unsaturated rings.

The high oxidation potential of benzoquinone is attributed not to the effect of unsaturation upon the strength of the carbonyl group as an oxidizing agent, but rather to the possibility given for isomerization of the initial reduced form (II) to a benzenoid system (III) for which the equilibrium is far to the right.



I II III

Thus the product of reduction (II) is in effect removed as it is formed, enabling more quinone to be oxidized. In the case of anthraquinone the position of the double bonds is stabilized by benzenoid rings. Hence, tautomerization cannot take place so easily and it consequently has a much higher reduction potential.

IV. Mechanisms.

Numerous mechanisms have been advanced to account for the ease ofinterchange of ketonic and alcoholic functional groups brought about by the use of aluminum alcoholates. Most of the theories have been modifications of Meerwein's original mechanism which was simply that an acetal-alcoholate was formed which broke down to a new alcoholate and a new carbonyl compound.

In the third column of Table III are given the changes in volts of the oxidation potentials of the carbonyl compounds with reference to the normal hydrogen electrode. These were calculated from the single electrode potential of [illegible] of the calomel electrode and the relative [illegible] of the [illegible]. [illegible] is [illegible]. The value of [illegible] is

[illegible]

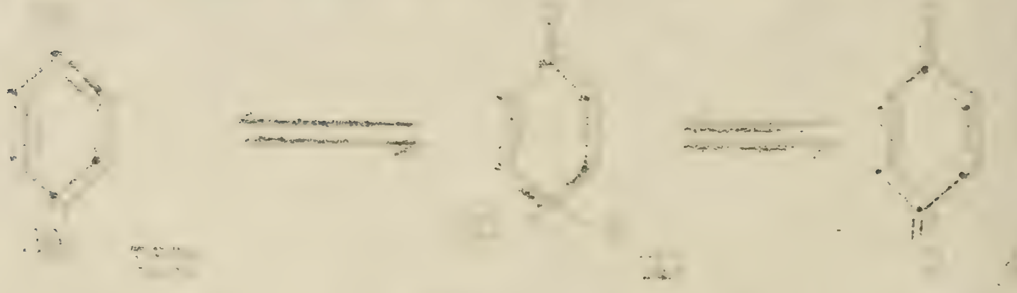
For cyclohexanone: [illegible]

[illegible]

Thus a consideration of the [illegible]

An interesting point that may be noted is the great diversity in structure among ketones which have similar oxidation potentials. [illegible]

The high oxidation potential of [illegible] is the effect of [illegible] upon the [illegible] of the carbonyl group [illegible] (III) for which the [illegible]



Thus the [illegible]

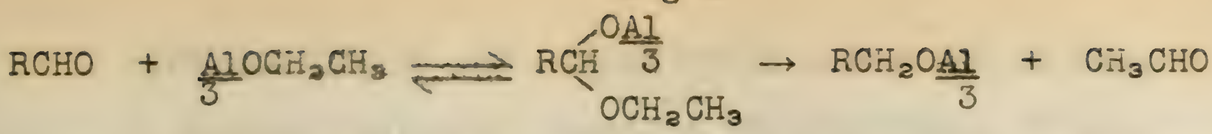
IV. Mechanism.

Various mechanisms have been advanced [illegible]

TABLE III

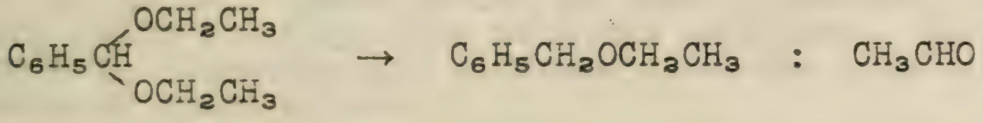
Carbonyl compound	Relative Activity	E_o v.
Camphor	2.03	0.115
Di-*i*-Pr ketone	1.00	.133
Di-*n*-Bu ketone	0.97	.134
Di-*n*-Pr ketone	.95	.134
Di-*i*-Bu ketone	.93	.135
Di-Et ketone	.68	.143
n-Pr Ph ketone	.62	.146
Me-cyclohexyl ketone	.56	.149
n-Bu Ph ketone	.55	.149
n-Am Ph ketone	.52	.150
Flourenone	.52	.150
Me Ph ketone	.51	.151
Et Ph ketone	.51	.151
Me-*t*-Bu ketone	.45	.154
Anthraquinone	.45	.154
Me Et ketone	.42	.156
Me *i*-Pr ketone	.42	.156
Cyclopentanone	.41	.156
Xanthone	.40	.157
i-Pr Ph ketone	.39	.158
Di-Me Ketone	.33	.162
Di-Ph ketone	.32	.163
1-chloroanthraquinone	.26	.168
		.174[a]
Cyclohexanone	.09	.195
Benzaldehyde	.08	.197
t-Bu Ph ketone	.07	.202
9,10-Phenanthrenequinone	3×10^{-6}	.460[a]
1,4-Napthoquinone	1×10^{-6}	.484[a]
1,4-Benzoquinone	1×10^{-10}	.715[a]
Diphenoquinone	4×10^{-15}	.954[a]

[a] These values are the potentials as determined by electrochemical methods. The last four relative reactivities were calculated from the value of E_o.



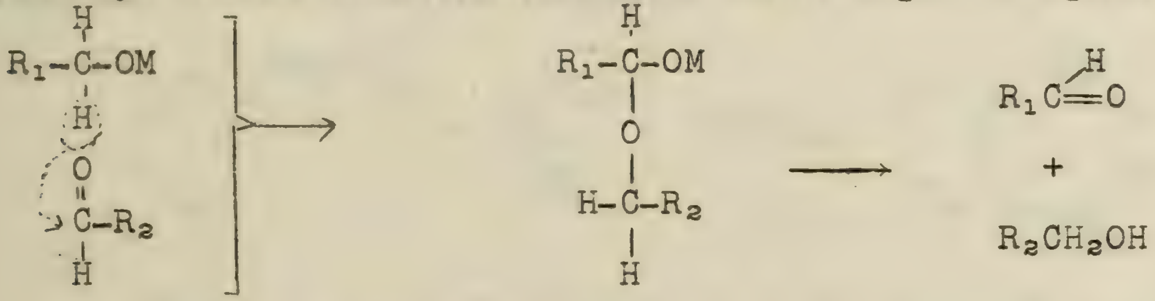
$$RCHO + \frac{Al}{3}OCH_2CH_3 \rightleftharpoons RCH\begin{array}{l} O\frac{Al}{3} \\ OCH_2CH_3 \end{array} \rightarrow RCH_2O\frac{Al}{3} + CH_3CHO$$

Evidence for this was that an intermediate addition compound could be isolated which was believed to have the acetal-alcoholate structure. It was known that the acetal given below broke down to give an ether and an aldehyde, and Meerwein reasoned that an acetal-alcoholate would break down in an analogous manner.

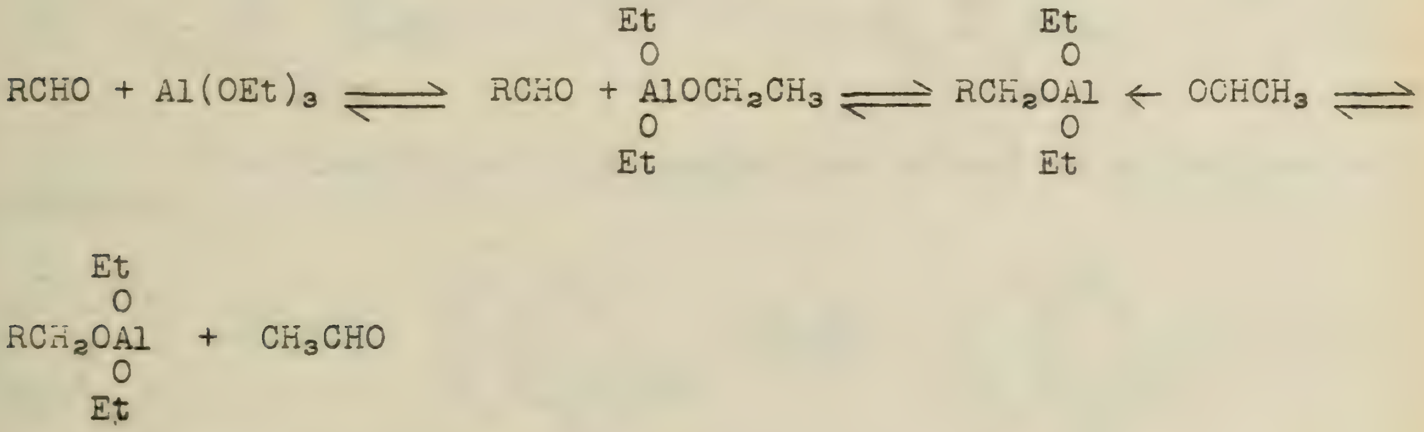


$$C_6H_5CH\begin{array}{l} OCH_2CH_3 \\ OCH_2CH_3 \end{array} \rightarrow C_6H_5CH_2OCH_2CH_3 \ : \ CH_3CHO$$

Ponndorf's theory postulates an unusual mode of addition to a carbonyl double bond (which is the chief argument against it).



Meerwein later advanced another mechanism, stating that his old one gave no good explanation for the role played by the metal alcoholate. From the known ability of aluminum to accept a pair of electrons to form coordinate addition compounds Meerwein considered it likely that compounds of the type $RCHO \rightarrow Al(OC_2H_5)_3$ are involved. He then formulated the reaction.



$$RCHO + Al(OEt)_3 \rightleftharpoons RCHO + \overset{\overset{Et}{O}}{\underset{\underset{Et}{O}}{AlOCH_2CH_3}} \rightleftharpoons \overset{\overset{Et}{O}}{\underset{\underset{Et}{O}}{RCH_2OAl}} \leftarrow OCHCH_3 \rightleftharpoons$$

$$\overset{\overset{Et}{O}}{\underset{\underset{Et}{O}}{RCH_2OAl}} + CH_3CHO$$

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Reported by T. E. Calmes, April 16, 1941

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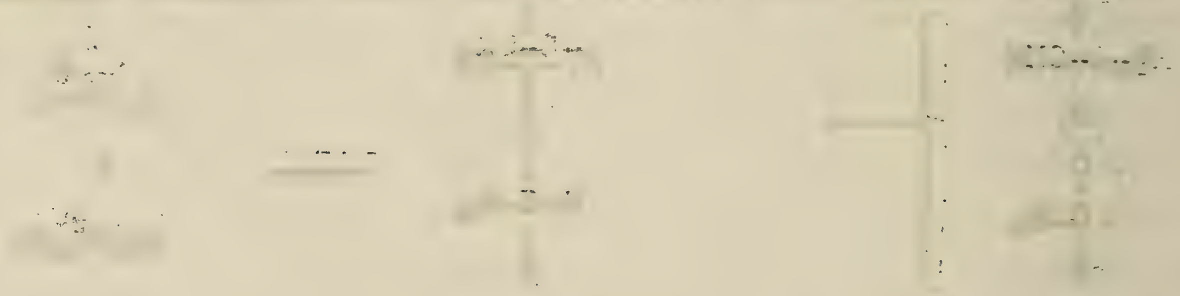

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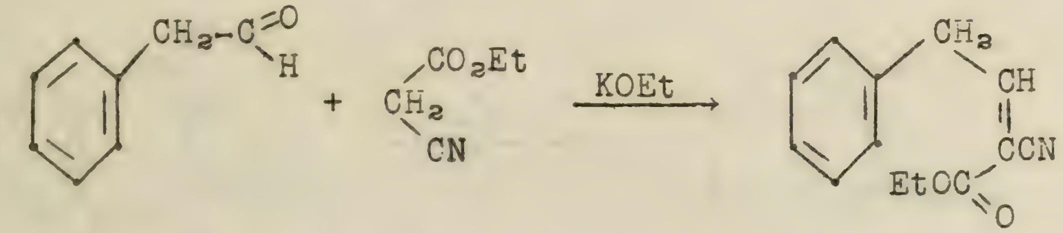
CYCLIZATION OF ARYL SUBSTITUTED ACIDS AND ESTERS

L. Marion, National Research Laboratories, Ottöwa
J.A. McRae, Queens University, Ontario

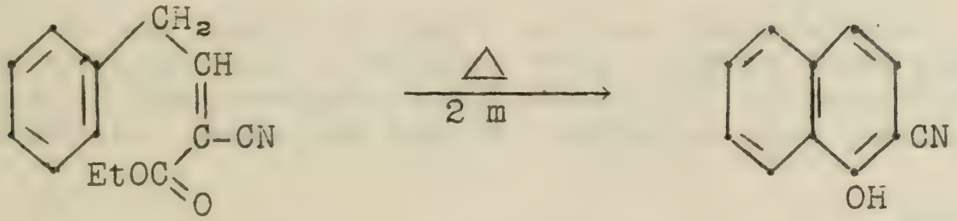
In the course of an investigation on the condensation product (1) of phenylacetaldehyde with ethyl cyanoacetate, McRae and Marion found that while this material could be distilled readily at 182°C. at 15 mm., distillation at lower pressures (2 mm.) led to foaming, with the formation of a new compound. This compound was phenolic in character and differed from the original material by the elements of ethyl alcohol.

The condensation of phenylacetaldehyde with ethylcyanoacetate may be indicated as follows:



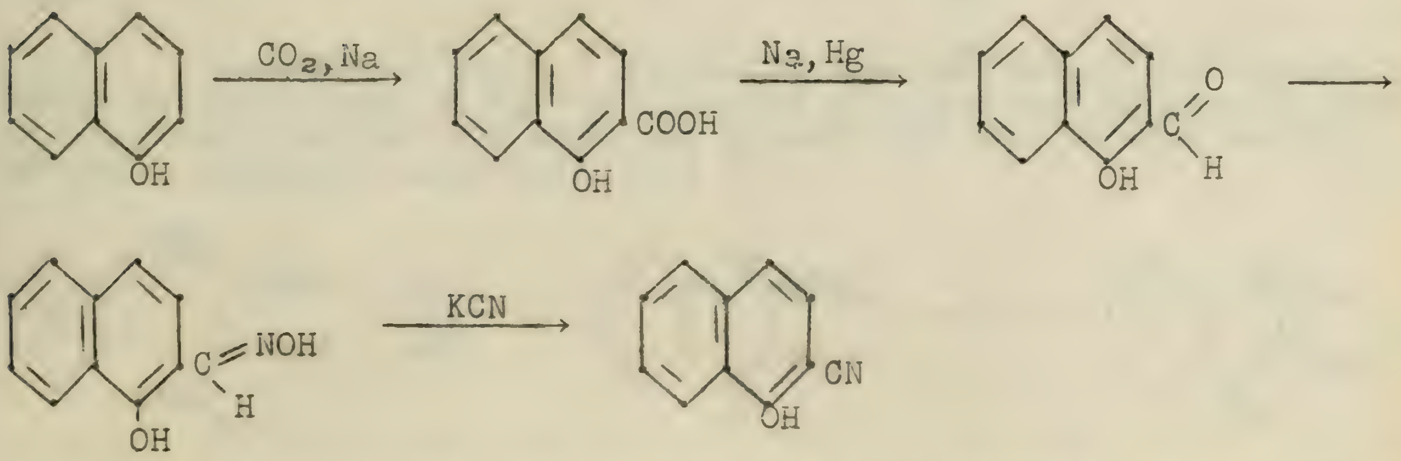
(1)

They explained the formation of the phenolic compound from this by postulating a ring closure by the splitting out of ethyl alcohol, with simultaneous migration of a hydrogen atom to form β-cyano-α-naphthol (2).

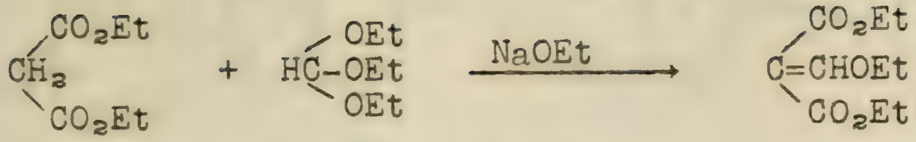


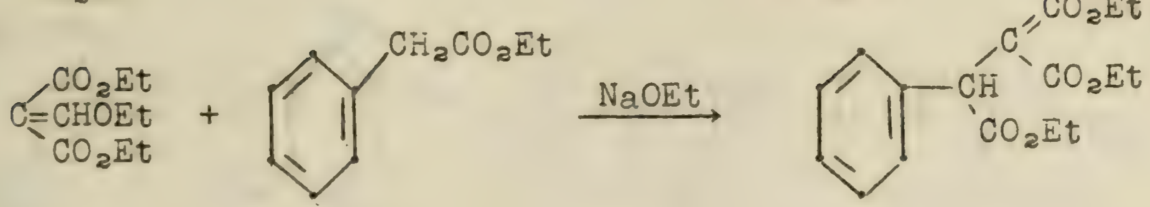
(2)

The identity of this product was proved by an independent synthesis:

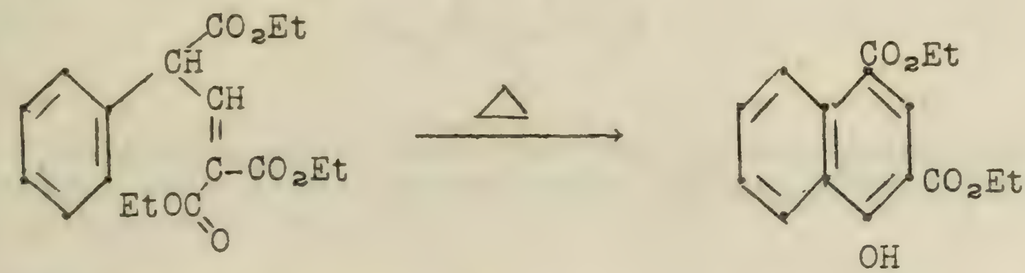


An analogous ring closure had been carried out earlier by Menon. He prepared ethyl-α,γ, dicarbethoxy-γ -phenylcrotonate (4) by condensing diethyl ethoxymethylenemalonate (3) with ethyl phenylacetate.


(3)

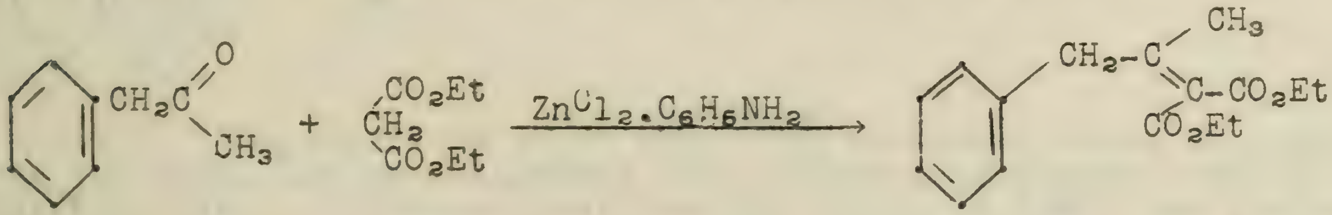

(4)

On attempted vacuum distillation or even on heating to 150°C the condensation product cyclized with the elimination of ethyl alcohol and the shifting of a proton.

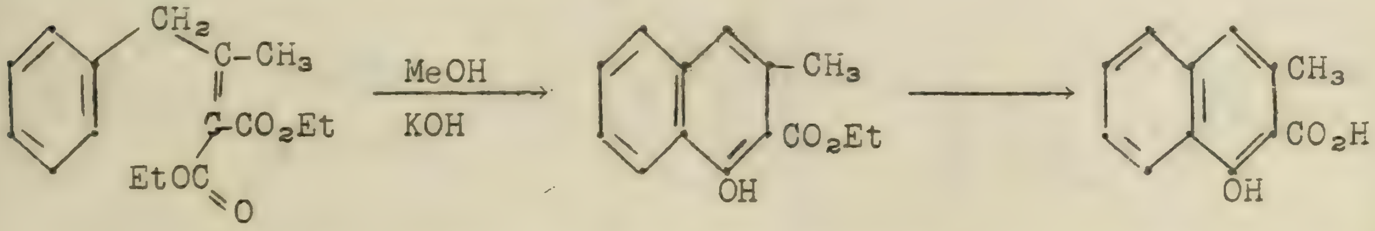

(5)

Menon also prepared 7-halo-1-naphthol-2-4-dicarboxylic acids by using ethyl p-halophenylacetate instead of ethyl phenylacetate in the above series of reactions.

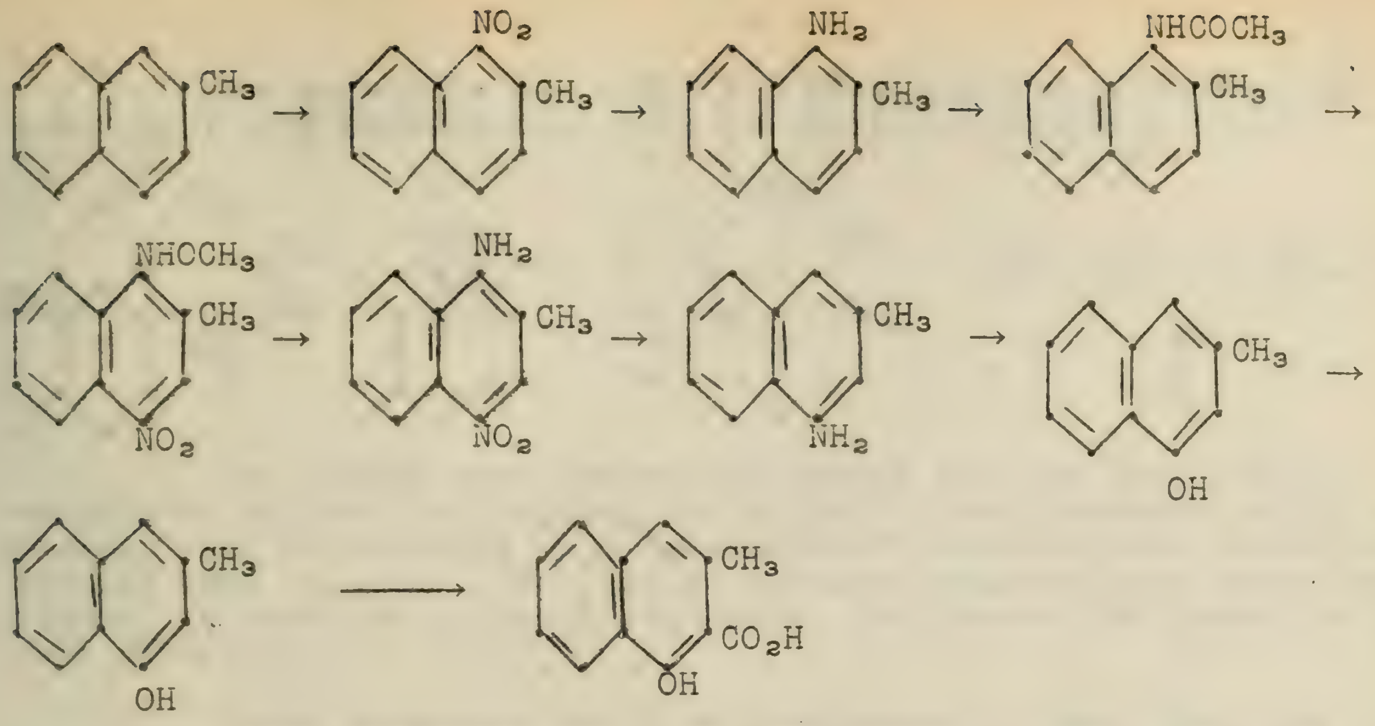
On the basis of their own and Menon's work, McRae and Marion correctly deduced that a similar ring closure took place on attempted hydrolysis of the condensation product (6) of phenylacetone and ethyl malonate. Hugh and Kon had prepared this product.


(6)

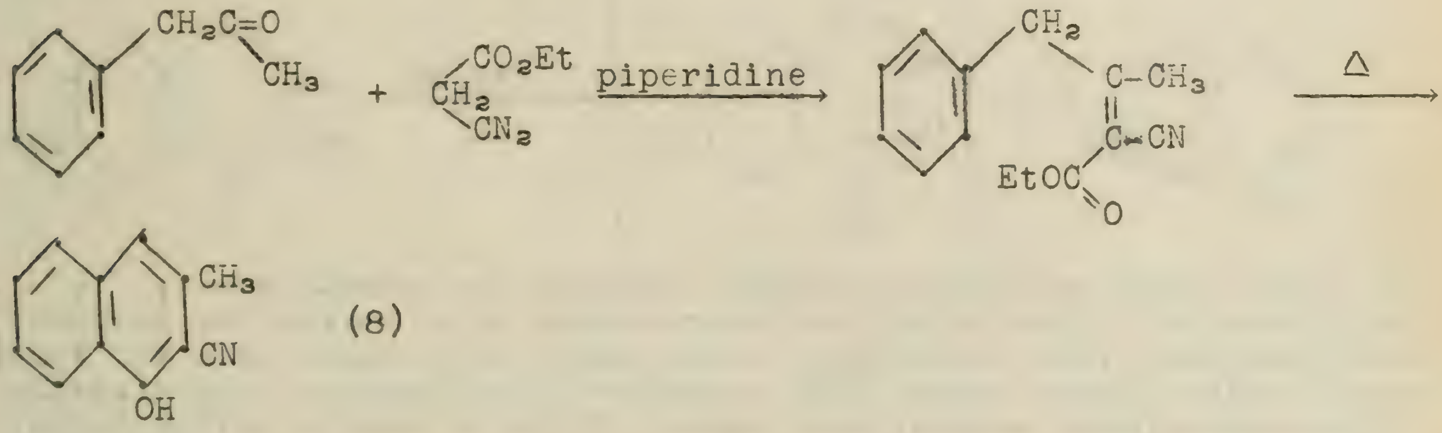
Hydrolysis did not yield the expected acid, but material which differed from it by the elements of water was obtained. McRae and Marion repeated this work and showed that the product was 3-methyl-1-hydroxy-2-naphthoic acid (7).


(7)

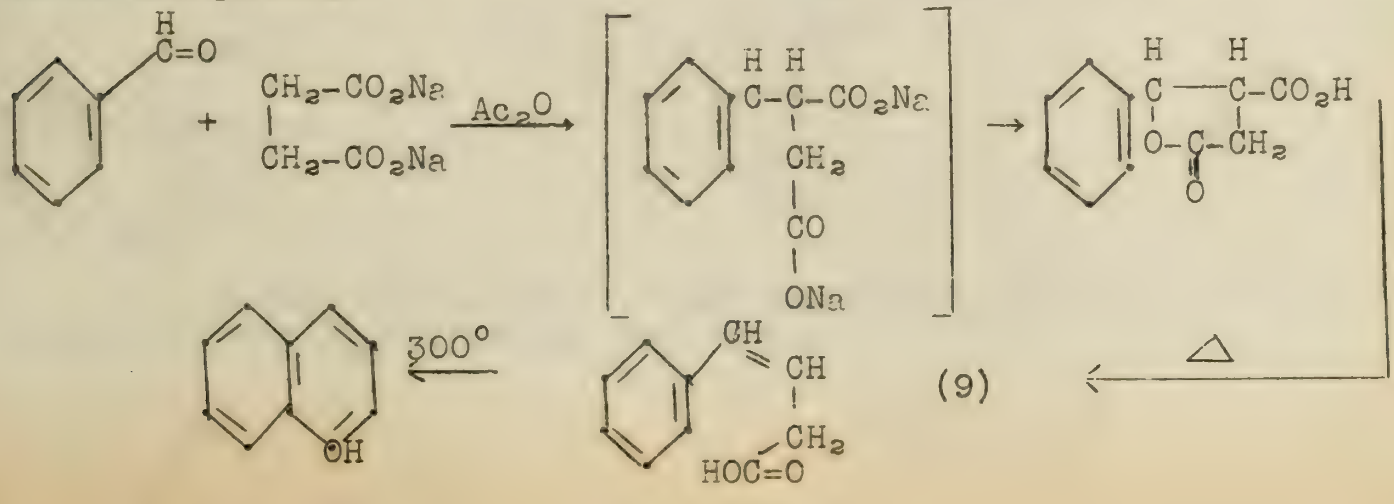
They synthesized this product by an independent method:



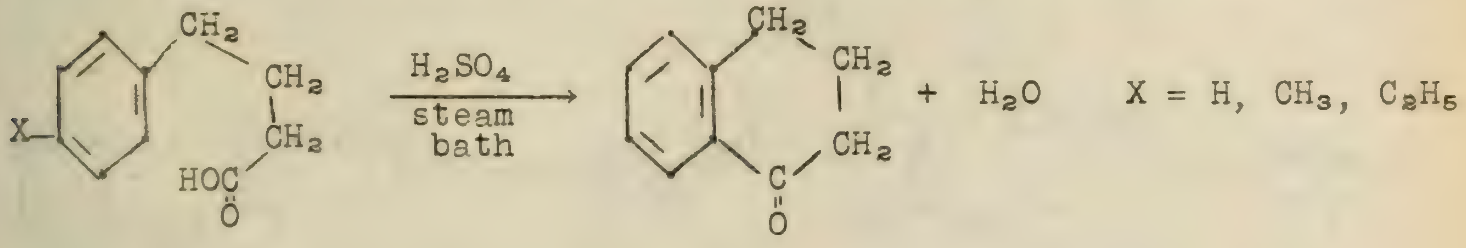
Similarly they found that the condensation product of phenylacetone with ethyl cyanoacetate (8) could be cyclized by heating in glycerol to 250°C.


(8)

The reactions which have been discussed above are comparable to the formation of α-naphthol from β-benzal propionic acid (9) on distillation. This was first done by Fittig in 1882. He prepared β-benzal propinic acid by a modified Perkin reaction using sodium succinate and acetic anhydride with benzaldehyde. On heating to 300°C this acid apparently distilled but the product collected in the receiver was insoluble in sodium carbonate and Fittig later showed it to be α-naphthol.

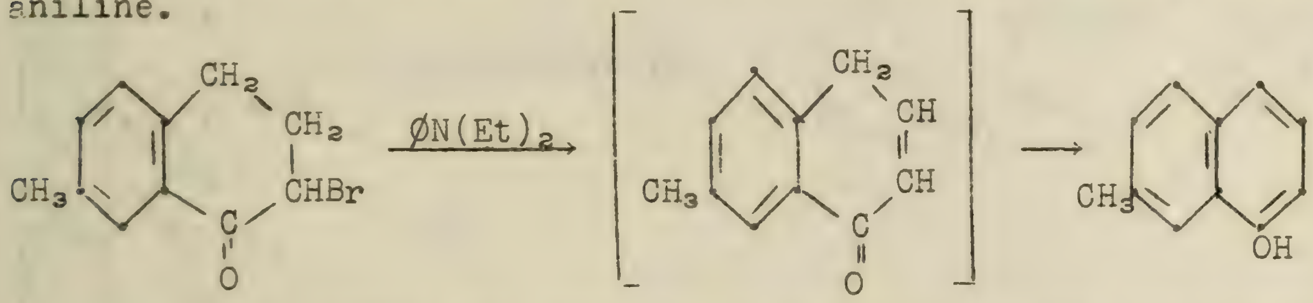

(9)

Krollpfeiffer has made keto tetrahydro naphthalenes by treating γ arylbutyric acids with concentrated sulfuric acid.

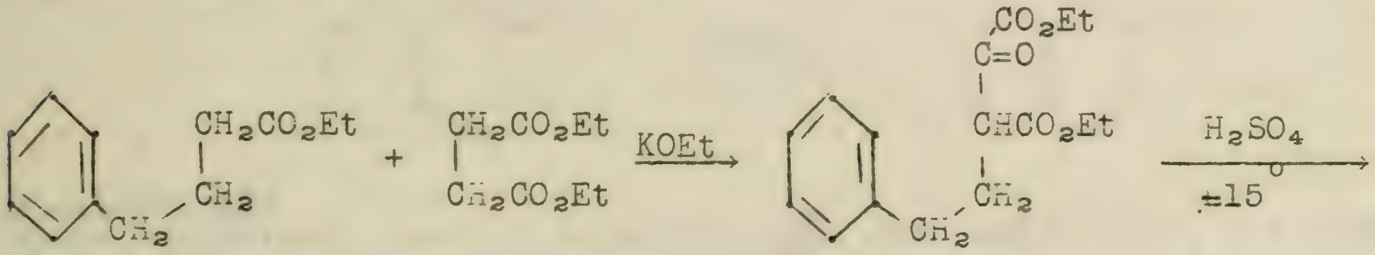


The yields were around 50% though in some cases small amounts of sulfonation reduced the yield. These products could, of course, also be obtained by a Friedel-Craft reaction with the corresponding acid chloride. The yields of this procedure for these compounds, as reported by Meyer and Stamm, are around 70% (based on the acid chloride).

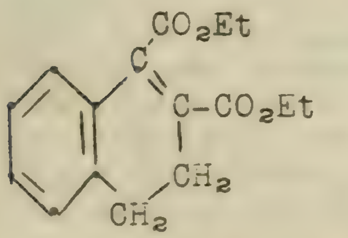
These compounds could be brominated in the 2 position by the action of bromine in carbon bisulfide, this bromo derivative could then be converted into a substituted naphthol by heating with diethyl aniline.



von Auwers has prepared dihydronaphthalene derivatives by treating ketoesters with concentrated sulfuric acid. He postulates that the ring closure in these cases takes place over the enol form. α-Ethoxalyl-γ-phenyl ethyl butyrate (10), when treated with concentrated sulfuric acid at -15°C yields 3-4-dihydro-1-2-dicarboethoxy naphthalene (11).



(10)



(11)

Higher temperatures yield increasing amounts of the anhydride of the corresponding free acid.

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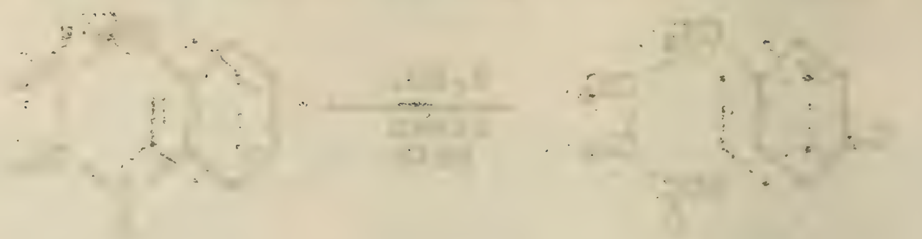

The yields were around [illegible] remarks of [illegible] mostly, also be [illegible] by a [illegible] acid [illegible]

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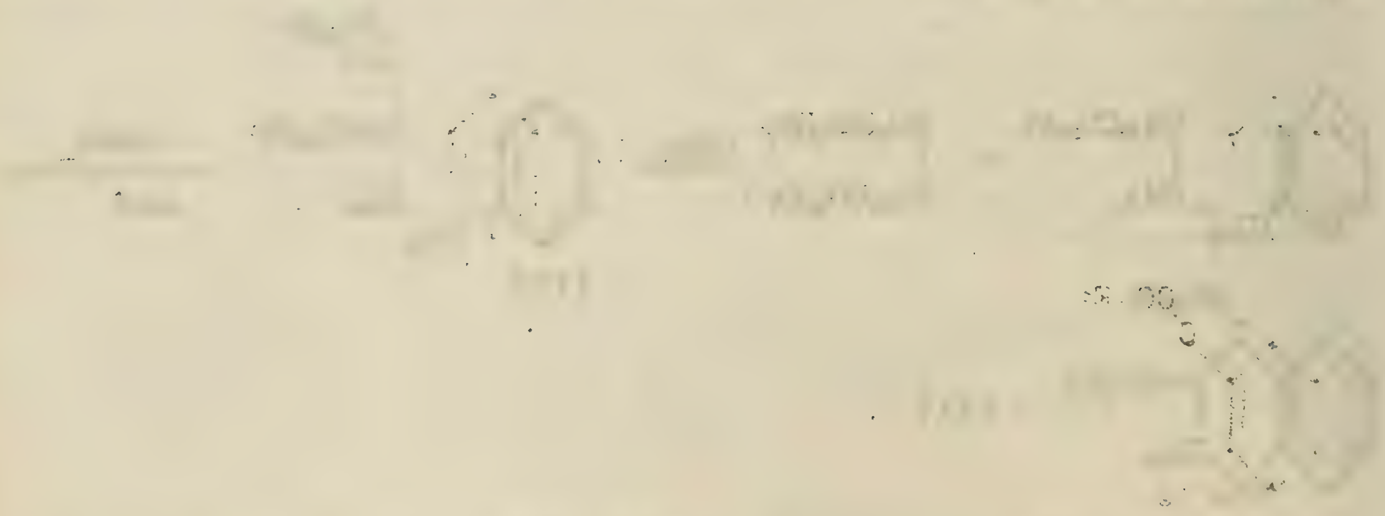

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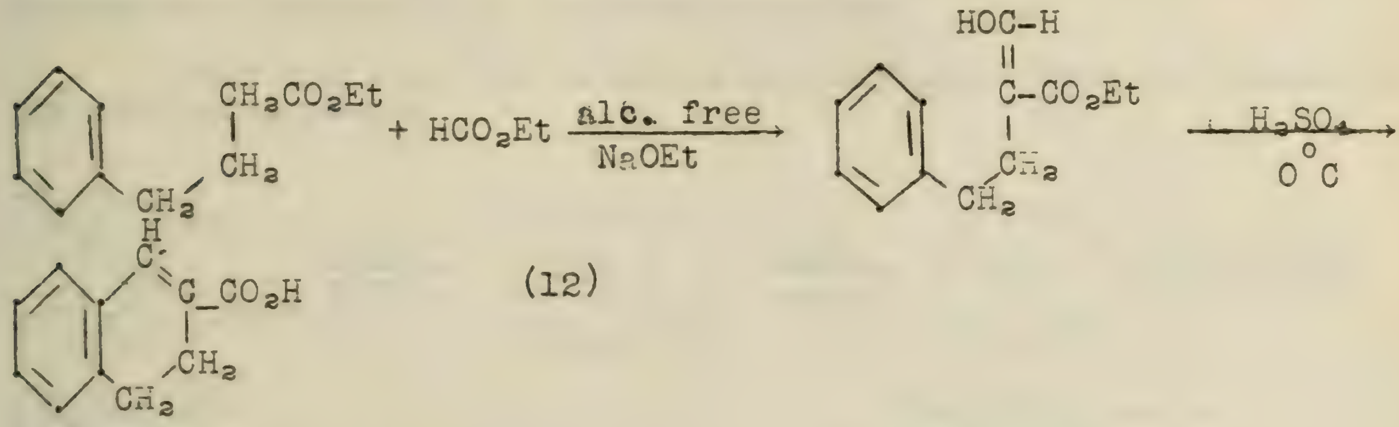
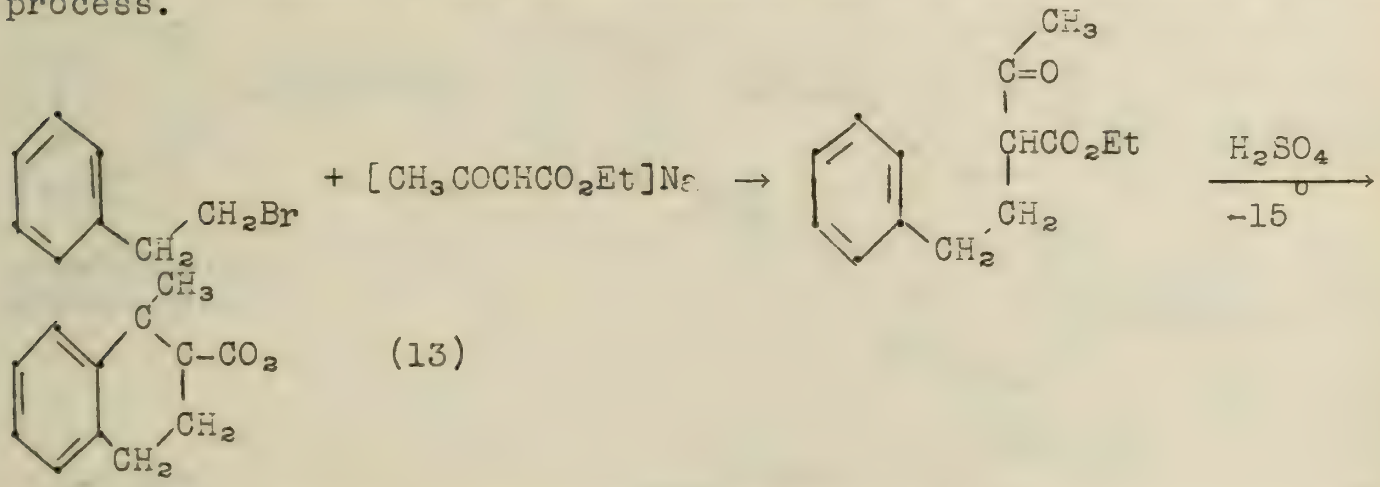
Similarly the condensation product (12) of ethyl formate with ethyl γ-phenylbutyrate is cyclized by sulfuric acid. von Auwers indicates this compound to be completely enolized.



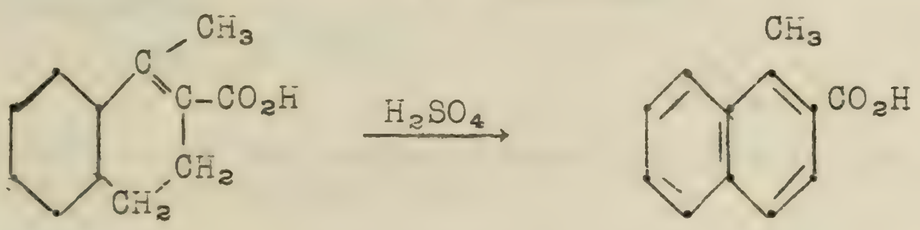
(12)

β-phenyl ethyl acetoacetate (13) is also cyclized by this process.



(13)

At higher temperatures the product to the naphthalene derivative.



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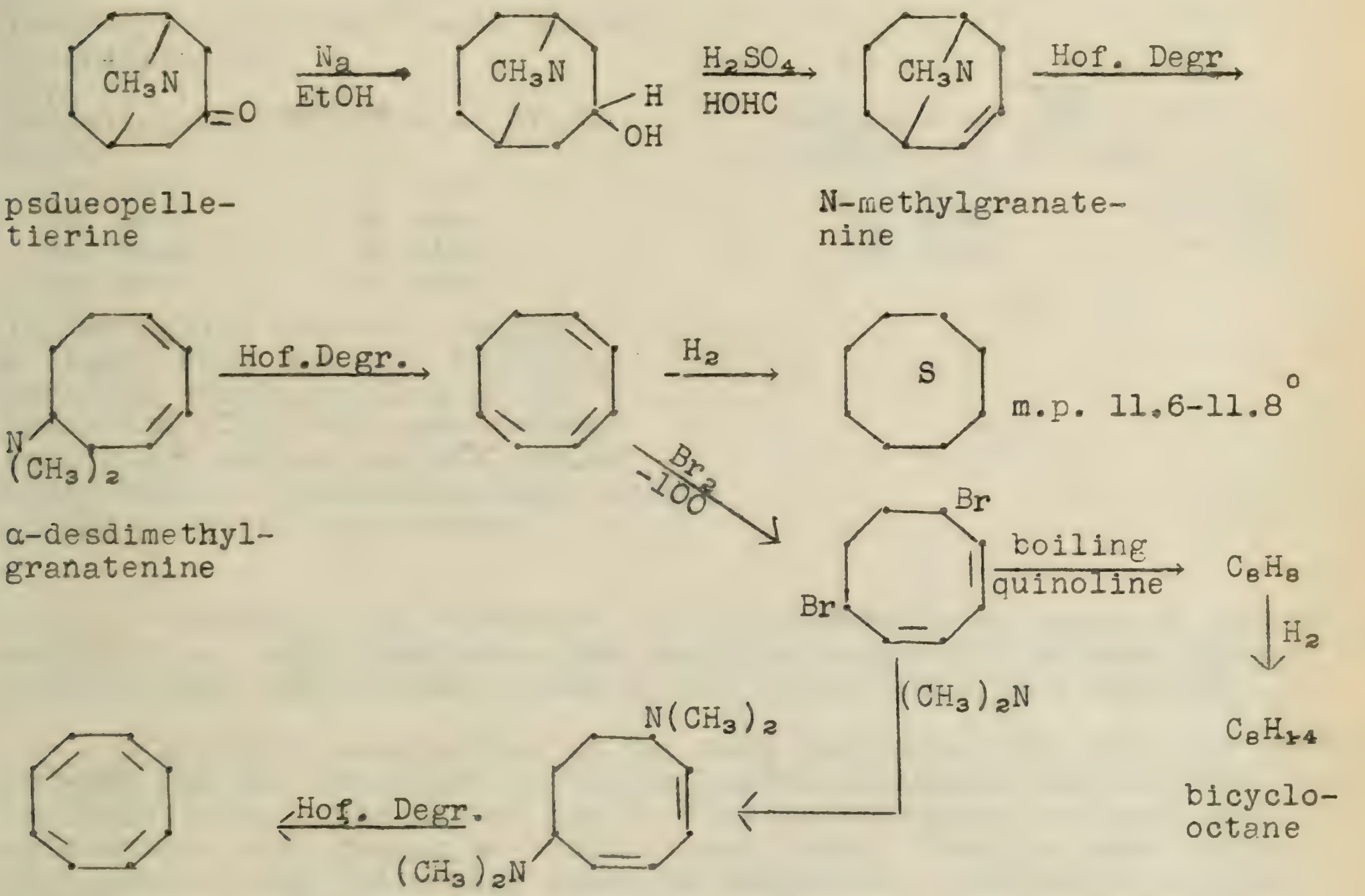
Reported by Chris Best
April 16, 1941

CYCLOOCTATETRAENE

One possible explanation for the aromatic character of benzene is the presence of a cyclic system of alternate double and single bonds. To investigate the validity of this theory, Willstatter undertook the preparation of the next higher ring system in which such an arrangement is possible, cyclooctatetraene.

Starting with the alkaloid pseudopelletierine he carried out the following steps:



The properties of the compound were definitely not aromatic and are listed in the following table:

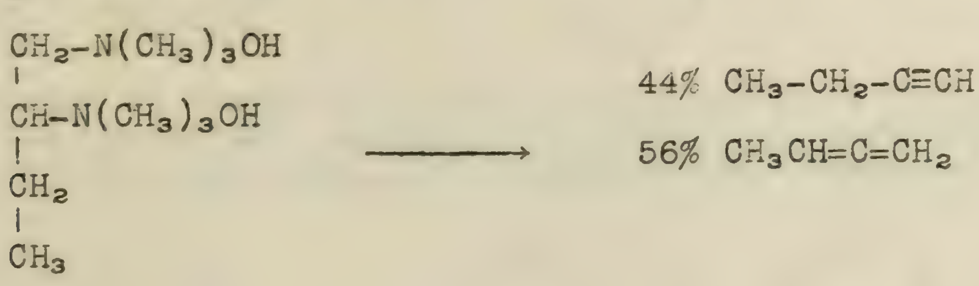
	Cyclooctatetraene		Styrene
B.P.	42.3° at 17 mm.		43° at 17 mm.
d_4^{20}	.909	$d_4^{19.9}$	.9073
n_D^{20}	1.539	n_D^{17}	1.543
Adds $Br_2 \rightarrow C_8H_8Br_2$	m.p. 70-71.5	ϕCH_2BrCH_2Br	m.p. 72-73°
The above brominates further with the loss of HBr →		$BrC_6H_4CH_2BrCH_2Br$	m.p. 60°

Table (Continued)

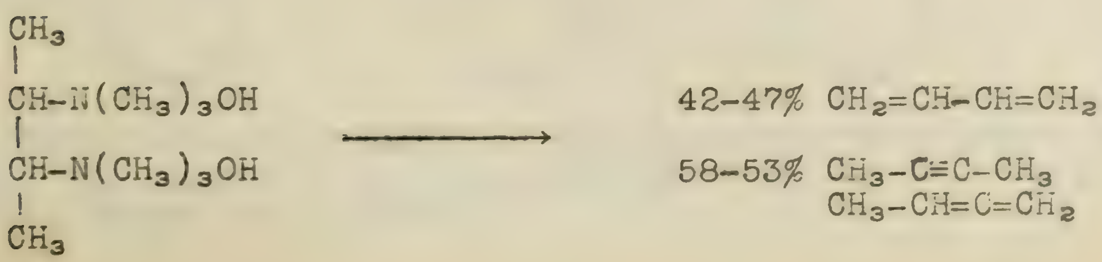
Cyclooctatetraene	Styrene
$C_8H_7Br_3$ m.p. 53-55°	
Adds HBr → C_8H_9Br B.P. 85-87°/12.5 mm.	ϕ $CHBrCH_3$ B.P. 97°/17 mm.
Treatment with nitric acid caused resinification	
Reduction in the presence of Pt black 1st mole 35 min. 2nd mole 40 min. 3rd mole 40 min. 4th mole 95 min.	Reduction of ϕH in the presence of Pt black 1st mole 24 min. 2nd mole 39 min. 3rd mole 37 min.
The reduction product remained a liquid with the most highly purified sample melting at 6.5°. Oxidation with HNO_3 gave suberic acid which melted low but, which after several crystallizations melted at the correct temperature.	

Willstatter's structure for the compound was accepted without any doubt up until 1938 when the striking similarity between cyclooctatetraene and styrene, shown in the above table, was noticed.

A closer examination of the work indicates that the only proof offered for the structure is the method of synthesis and the reduction to cyclooctane. The latter can be disregarded since any unsaturated cyclooctane will reduce to cyclooctane. Hurd, from his work on the pyrolysis of his quaternary ammonium hydroxides, related to 1,2 and 2,3-butenes criticizes the method of synthesis. Hurd obtained the following results:

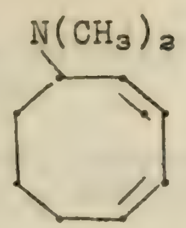


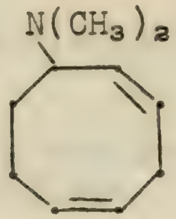
$$\begin{array}{l} \mathrm{CH_2-N(CH_3)_3OH} \\ | \\ \mathrm{CH-N(CH_3)_3OH} \\ | \\ \mathrm{CH_2} \\ | \\ \mathrm{CH_3} \end{array} \longrightarrow \begin{array}{l} 44\%\ \mathrm{CH_3-CH_2-C{\equiv}CH} \\ 56\%\ \mathrm{CH_3CH=C=CH_2} \end{array}$$

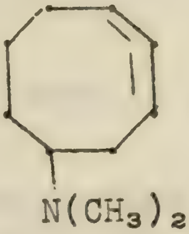


$$\begin{array}{l} \mathrm{CH_3} \\ | \\ \mathrm{CH-N(CH_3)_3OH} \\ | \\ \mathrm{CH-N(CH_3)_3OH} \\ | \\ \mathrm{CH_3} \end{array} \longrightarrow \begin{array}{ll} 42\text{-}47\% & \mathrm{CH_2=CH-CH=CH_2} \\ 58\text{-}53\% & \mathrm{CH_3-C{\equiv}C-CH_3} \\ & \mathrm{CH_3-CH=C=CH_2} \end{array}$$

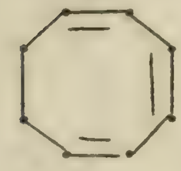
He postulated that in Willstatter's synthesis the following compounds were possible in the first Hofmann degradation.

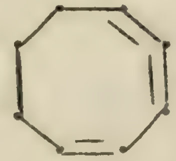


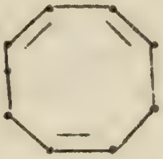




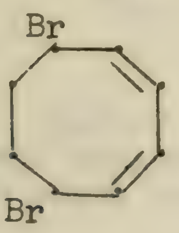
These would give the following trienes --

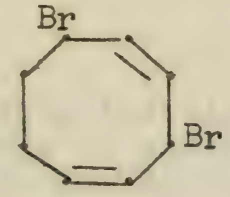


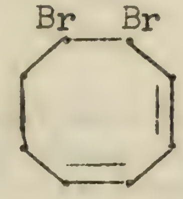


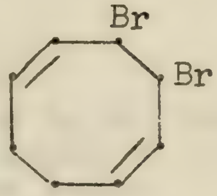


The conjugated triene on bromination would give --

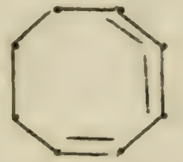




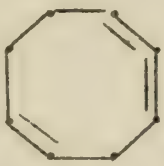




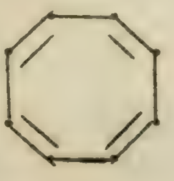
If the other two trienes are included one would obtain fourteen such dibromides. Treatment with $(CH_3)_2$ N gave Willstatter a mixture of amines consisting of a diamine stable towards acids and one that was not. This last hydrolysis pointed to the presence of the $C-C=C-N(CH_3)_2$ group which Hurd claims could only arise from the dibromides from

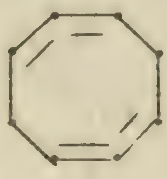


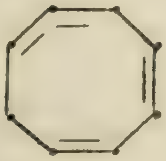
and



The presence of these two isomers would indicate that all other isomers are possible. Assuming that only the desired diamine is present in the next step, the following would result.







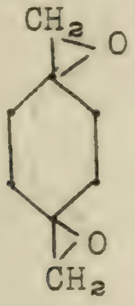
Willstatter's method is being repeated by Linstead at Harvard. The source of pseudopelletierine is the following reaction devised by Schopf and Lehrmann.

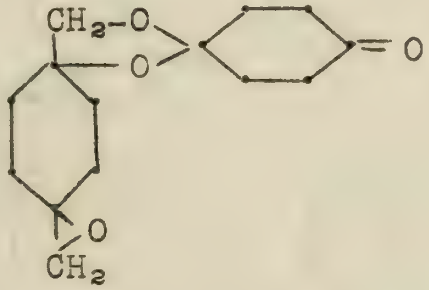
$$CH_2(CH_2CHO)_2 + CO(CH_2COOH)_2 + CH_3NH_2 \xrightarrow[\text{5 days}]{\text{PH = 7}}$$ 95% yield of pseudopelletierine (phosphate buffer)

Other methods of synthesizing cyclooctatetraene have been tried recently.

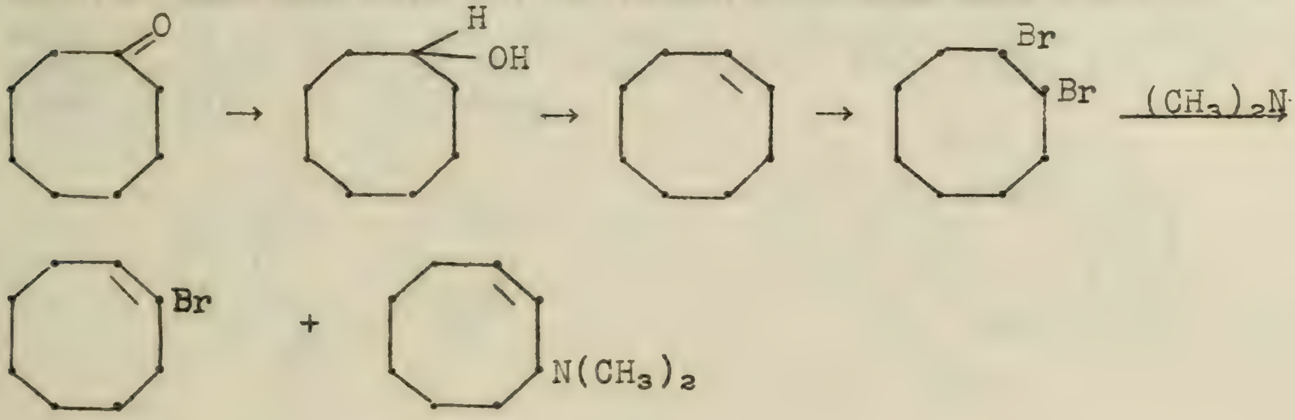
Taylor, dehydrogenating cyclooctene over chromic oxide at 400° obtained a 92% yield of styrene.

Vincent, attempting to synthesize 1,5-cyclooctandione by treating 1,4-cyclohexanedione with diazomethane obtained four products two of which were identified as the following:



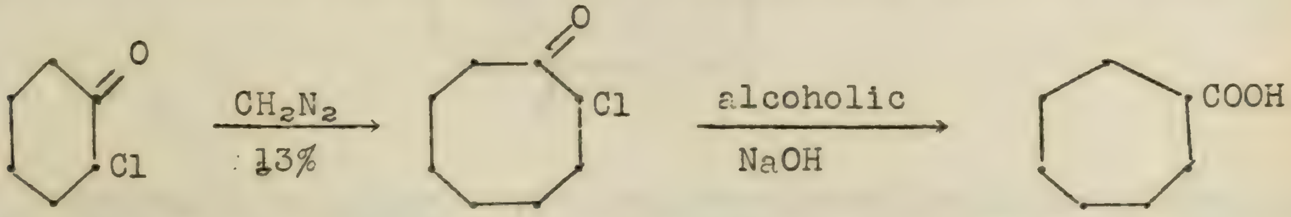


Kohler applying the diazomethane reaction to cycloheptanone obtained cyclooctanone in workable amounts. Attempts to introduce unsaturation ran into the difficulties summarized below.



very small amount

Treatment of α-chlorocycloheptanone with diazomethane gave a 13% yield of α-chlorocyclooctanone. Treatment with alcoholic alkali caused the Favorskii degradation to cycloheptane carboxylic acid.



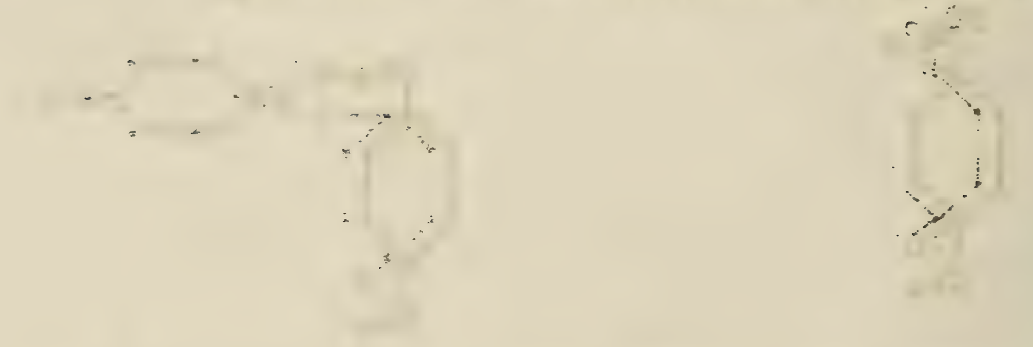
A new approach to the problem is the synthesis of substituted cyclooctatetraenes. These compounds may be easier to make and yet serve for the purpose of determining whether the ring is aromatic or not.

[illegible] + [illegible] → [illegible]

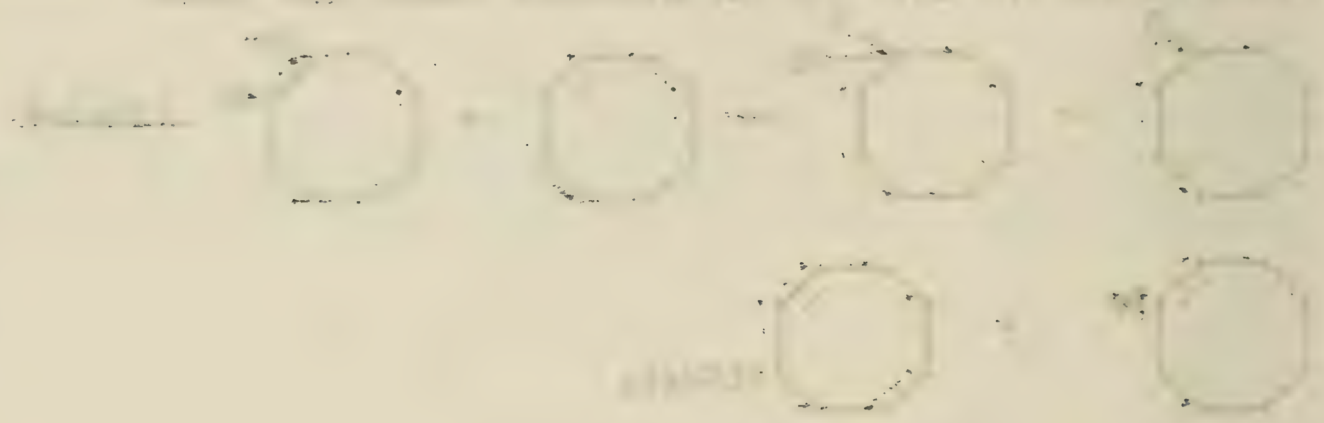
Other methods of [illegible] were tried unsuccessfully.

a. [illegible] and obtained a [illegible] yield of [illegible].

Recently, attempting to [illegible] by treating [illegible] with [illegible] obtained [illegible] the [illegible] identified as the following:



Kohler applying the [illegible] reaction [illegible] obtained [illegible] in [illegible] although [illegible] the [illegible].

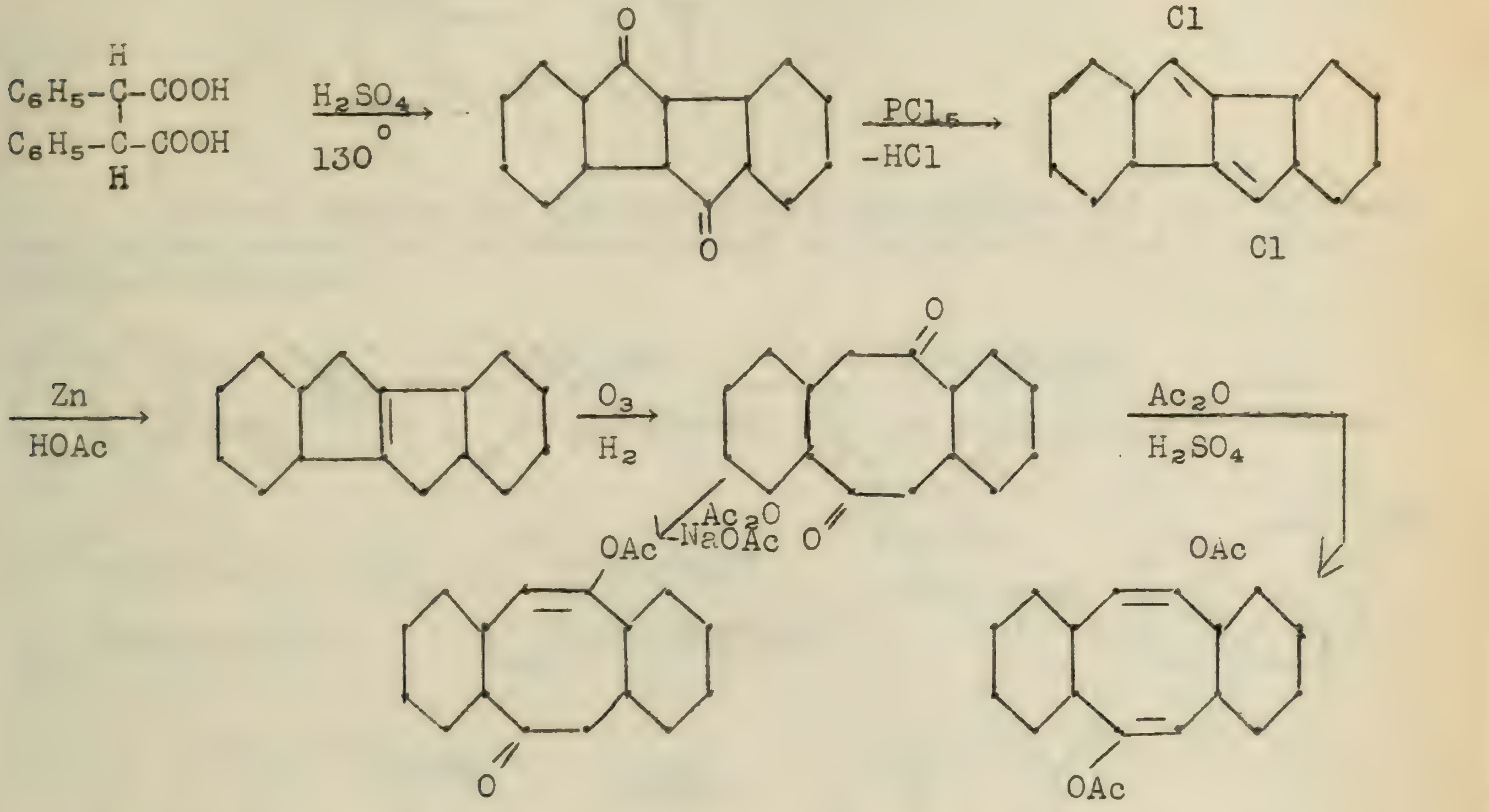


very small amount

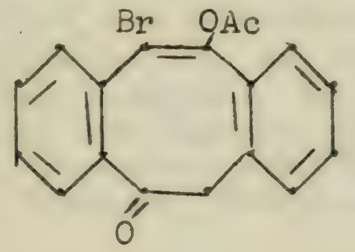
Treatment of o-chlorocyclohexanone [illegible] gave a [illegible] yield of [illegible]. [illegible]

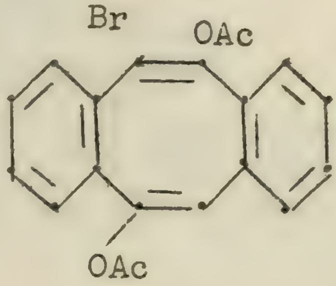
A [illegible] of the [illegible] in the [illegible] of [illegible]. [illegible] that the presence of [illegible]

One synthesis which has led to a rather highly substituted cyclooctatetraene is the following:

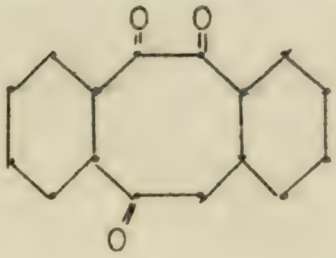


The behavior of this substituted cyclooctatetraene with bromine is peculiar and can best be demonstrated by comparing its behavior with that of the monoacetate. Both substitute one bromine atom to give the following:

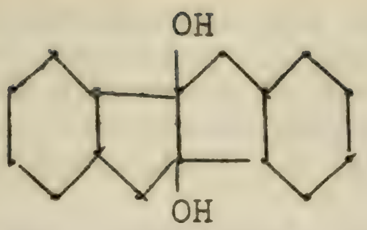




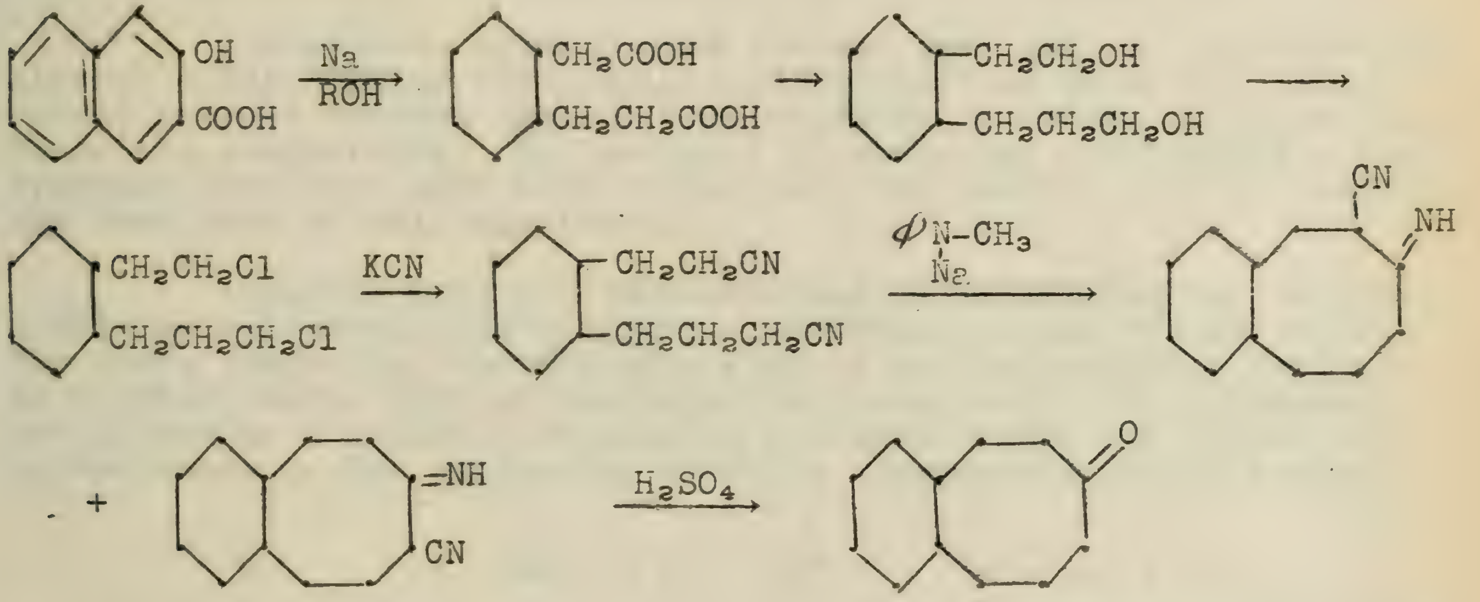
The monobromidiacetate is resistant to further bromination whereas the monobromomonoacetate adds bromine to give a product which could be hydrolyzed to



Attempts to prepare sym-dibenzocyclooctatetraene by reducing the diketone and dehydrating were failures due to the ease with which the compound bridges to a bicyclooctane derivative.



Fieser working in the same field has carried out the following preliminary steps in a synthesis which he hopes will lead to benzocyclooctatetraene.



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Vincent, Thompson and Smith, J. Org. Chem., 3, 603 (1939).

Kohler, Tishler, Potter and Thompson, J. Am. Chem. Soc., 61, 1057 (1939).

Steadman, ibid., 62, 1607 (1940).

Wawzonek, ibid., 62, 745 (1940).

Fry and Fieser, ibid., 62, 3489 (1940).

Reported by S. Wawzonek
April 23, 1941

CYANINE DYES

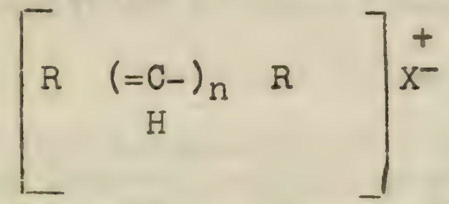
The first cyanine dye was prepared by Grenville Williams in 1856. From the reaction of amyl iodide and ammonia on quinoline he isolated a blue dye which he called cyanine. The quinoline contained lepidine (__-methylquinoline as an impurity. The essential constituents were quinoline, lepidine and any alkyl iodide.

The great commercial value of the cyanines lies in their power of conferring extra sensitivity to the photographic plate. The recent improvement in high speed panchromatic, red, and infrared film is due in a large part to the development of suitable cyanine dyes.

In general cyanine dyes are not fast and are sensitive to mineral acids, making them useless in the textile industry. A few recent patents concern cyanine dyes suitable in dyeing textiles, but these are exceptional. In the field of bacterial antiseptics a few cyanines have been used with marked success; however, little research has been done on this application.

Cyanine dyes are characterized by possessing two heterocyclic nuclei containing nitrogen. According to the static formula for these compounds, the nitrogen atom of one heterocyclic nucleus is tertiary while that of the other is quaternary. The nitrogens are joined by a chain of conjugated linkages; hence the number of carbon atoms in the conjugated chain is necessarily an odd number.

I

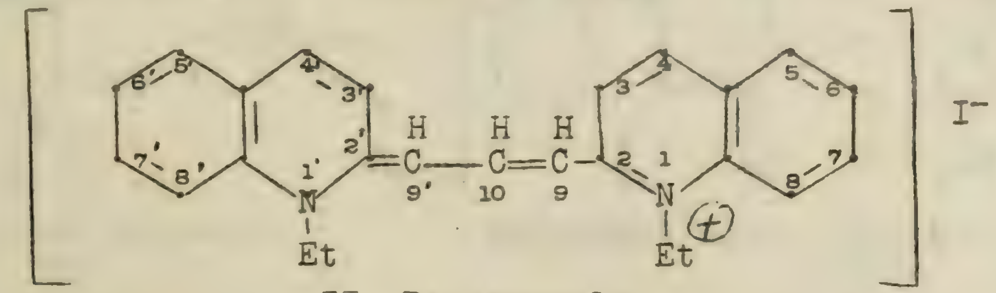


$$\left[R\ (\underset{H}{=C-})_n\ R \right]^{+} X^{-}$$

n = 1,3,5,7,11
R = heterocyclic nucleus containing nitrogen

A large number of heterocyclic nuclei have been investigated and the properties of the corresponding cyanine dyes recorded. Some of the more common and useful cyanines contain the quinoline, pyridine, benzothiazole, benzoselenazole, and naphthothiazole nuclei.

Pinacyanole (1,1'-diethyl-2,2'-carbocyanine iodide) is an example of a carbocyanine. It is a well known commercial sensitizer and also an extremely potent antiseptic for Staphylococci.



II Pinacyanole

The usefulness of a given cyanine dye is dependent on the spectral region in which it sensitizes the photographic emulsion. This region of sensitization is directly related to the absorption maximum of the dye. In addition to this factor, sensitizing dyes behave very differently with various types of photographic emulsions.

A successful dye must not only have the required absorption maximum, but also must give an emulsion free of fog, and relatively stable.

Factors which influence the absorption maximum of the dye are listed below:

1. nature of the heterocyclic nucleus
2. substituents on the heterocyclic nucleus.
3. nature of the N-alkyl group.
4. number of carbon atoms in the conjugated polymethinyl chain.
5. substituents on the polymethinyl chain.

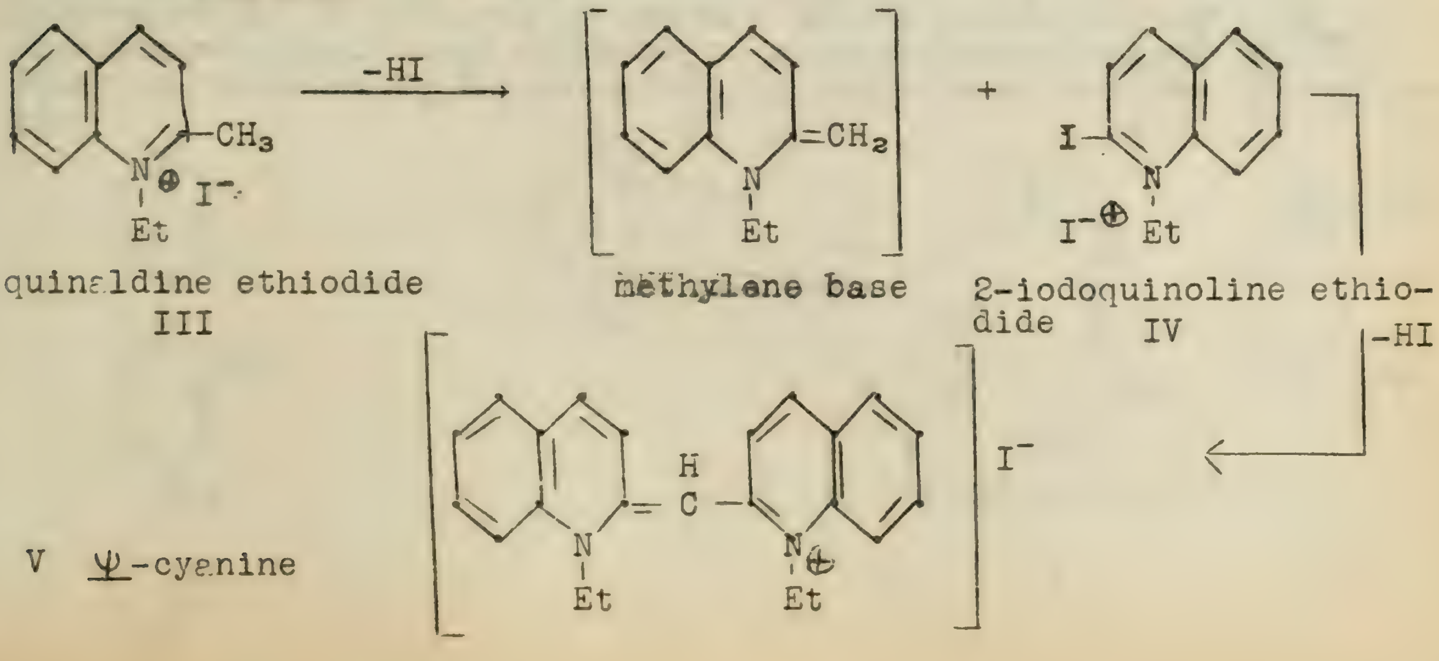
As long as the anion of the dye is colorless it has no effect on the absorption maximum.

The most potent factor in obtaining dyes which will sensitize in the far infrared is the length of the conjugated polymethinyl chain. From a synthetic point of view, increase in chain length involves a great deal of preparative difficulty. Recently a number of dicarbocyanines (n = 5) and tricarbocyanines (n = 7) have been prepared. The most recent addition is a pentacarbocyanine (n = 11), which sensitizes in the extreme infrared above 10,000 A.

Synthetic Methods

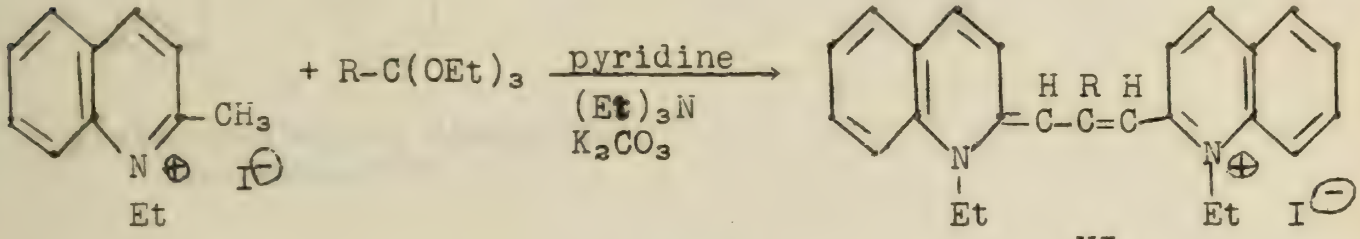
Cyanine dye condensations are carried out in pyridine solution containing triethylamine. Absolute alcohol is sometimes added for its solvent action. The reactants are refluxed less than one hour and the product is then isolated and purified. Recent patents describe the use of solid K_2CO_3 in the reaction mixture to take up the HX formed in the reaction. Under the proper conditions the yield ranges from 40 to 70% of pure product.

Synthesis of a ψ cyanine (V)



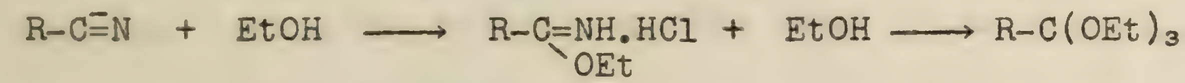
Synthesis of Carbocyanines (n= 3)

Quinaldine ethiodide is condensed with ethyl orthoformate under the conditions mentioned above. The orthoformic ester can be replaced with formaldehyde, CHX_3 and trioxymethylene. To prepare carbocyanines substituted in the methinyl chain, the ethylorthoformate is replaced with alkyl and aryl orthoesters.



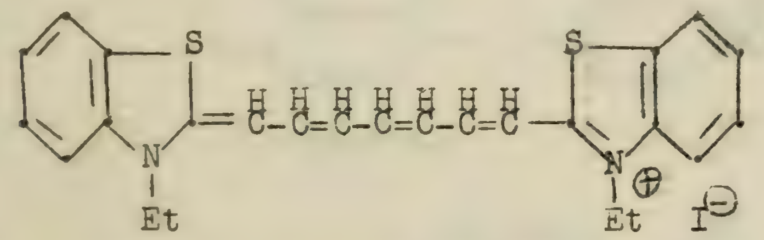
VI

The orthoesters for this condensation are conveniently prepared from the corresponding nitriles by conversion to the iminoether hydrochlorides, and then to the orthoester.

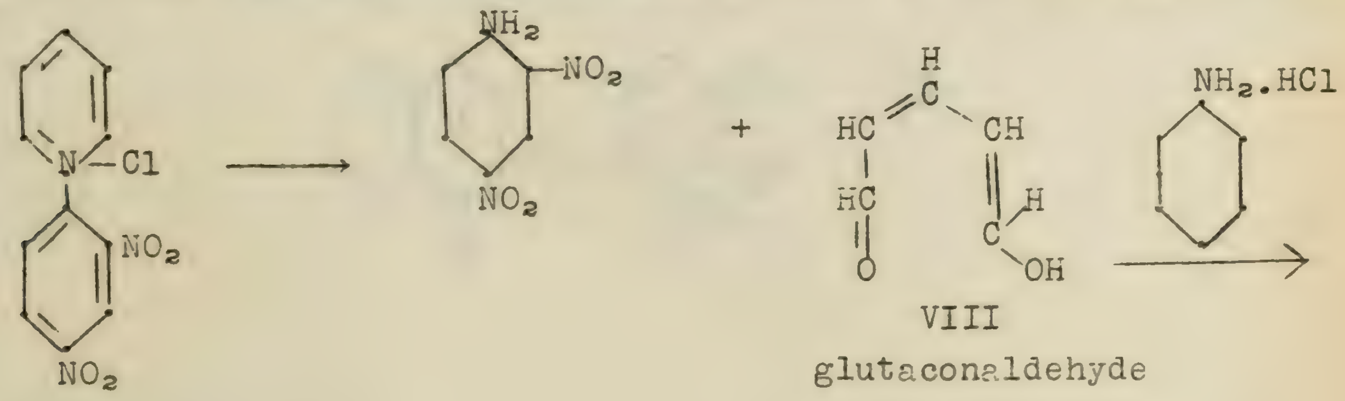


$$R-C\equiv N \;+\; EtOH \longrightarrow R-\underset{OEt}{C}=NH.HCl \;+\; EtOH \longrightarrow R-C(OEt)_3$$

The synthesis of the tricarbocyanine, 2,2'-diethyl,1,1'-benzothioazoletricarbocyanine iodide (VII) is especially interesting.

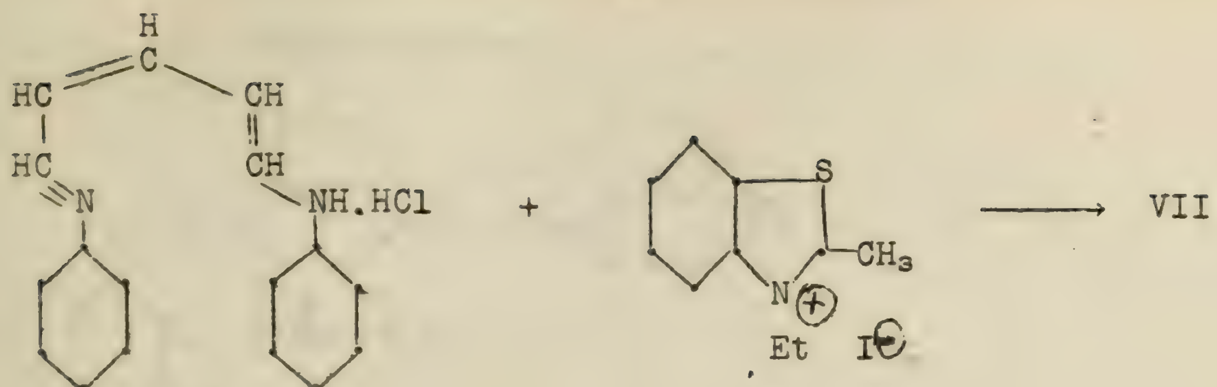


It is prepared from 1-methylbenzotioazole ethiodide (X) and glutaconaldehyde dianilide hydrochloride (IX) in 50% yield. The dianilide hydrochloride is prepared by rupture of the pyridine ring in 2,4-dinitrophenylpyridinium chloride to give glutaconaldehyde (VIII) which is isolated as the dianilide by addition of aniline hydrochloride.



VIII

glutaconaldehyde



IX
glutaconaldehyde dianilide
hydrochloride

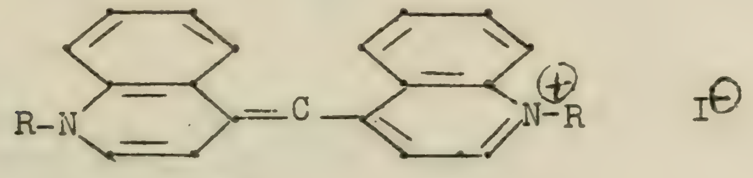
X

TABLE I

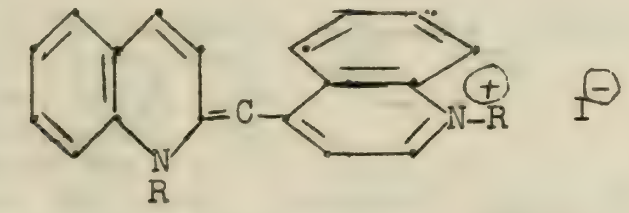
Classification of a Few Common Cyanines Containing the Quinoline Nucleus

A. Cyanines having one methinyl carbon atom

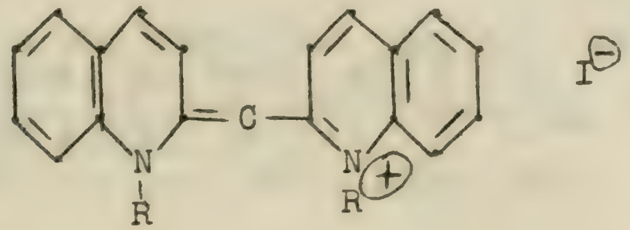
1. true cyanines



2. isocyanines

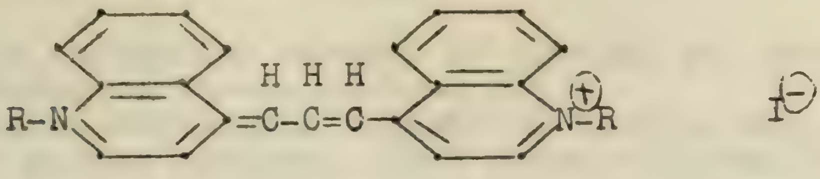


3. ψ or pseudocyanines

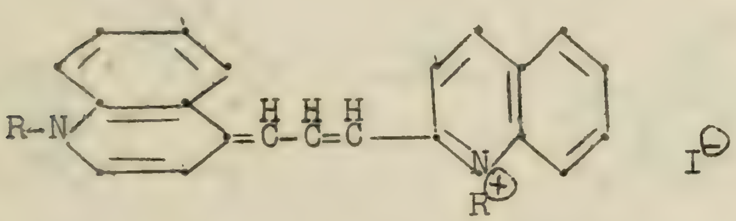


B. Cyanines Having Three Methinyl Carbon Atoms

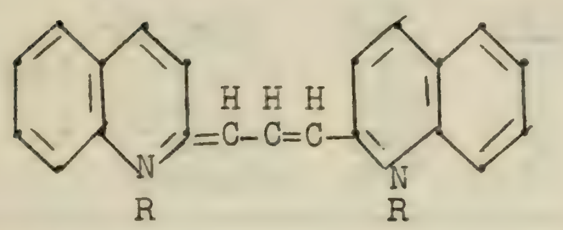
1. kryptocyanines



2. "dicyanines"



3. carbocyanines



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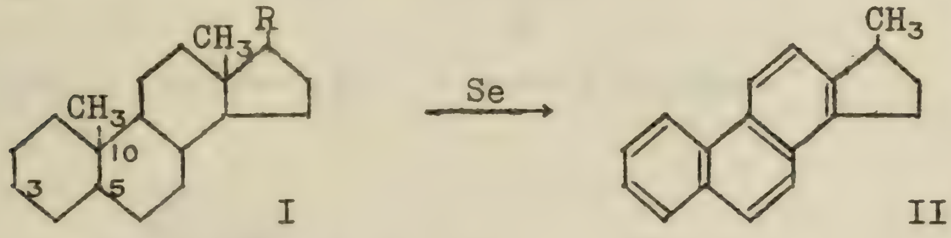
Reported by C.M. Himel
April 23, 1941

THE STRUCTURE OF THE STEROID SAPOGENINS

Marker - Pennsylvania State College

Sapogenins, which are isolated from plants as glycosides (saponins), are divided into two classes:

I. Steroid sapogenins contain 27 carbons and have a cyclopentanoperhydrophenanthrene nucleus (I).
II. Triterpene sapogenins contain 30 carbons and are considered to have a picene nucleus. This group will not be considered in this report.



The following table lists the monohydroxy steroid sapogenins.

Sapogenin	Formula	M.P.	$[\alpha]_D$	Original Source
Sarsasapogenin	$C_{27}H_{44}O_3$	199°	-60	Jamaica sarsaparilla root
Smilagenin	$C_{27}H_{44}O_3$	184°	-61	Jamaica sarsaparilla root
Tigogenin	$C_{27}H_{44}O_3$	204°	-49	Digitalis (foxglove)
Diosgenin	$C_{27}H_{42}O_3$	202°	-129	Dioscorea (in Japan)

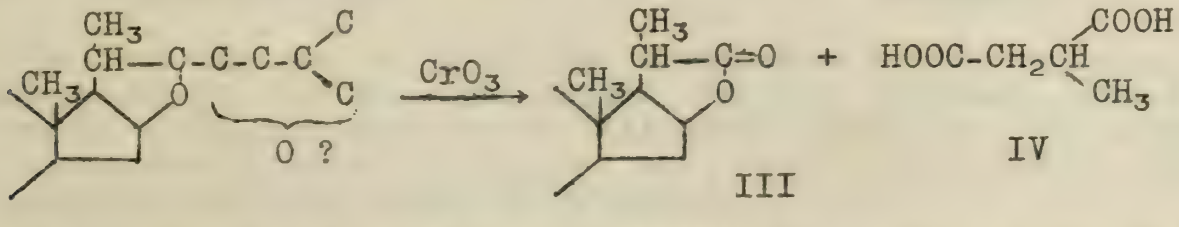
In addition, the dihydroxy sapogenins gitogenin and chlorogenin (both $C_{27}H_{44}O_4$) and the trihydroxy digitogenin ($C_{27}H_{44}O_5$) have been characterized and the positions of the additional hydroxyls determined. In all of the sapogenins, two of the oxygens are in the side chain and are relatively unreactive.

Up to 1938 the significant results obtained from investigations of the monohydroxy sapogenins were as follows:

1) Dehydrogenation gave Diels' hydrocarbon (II).

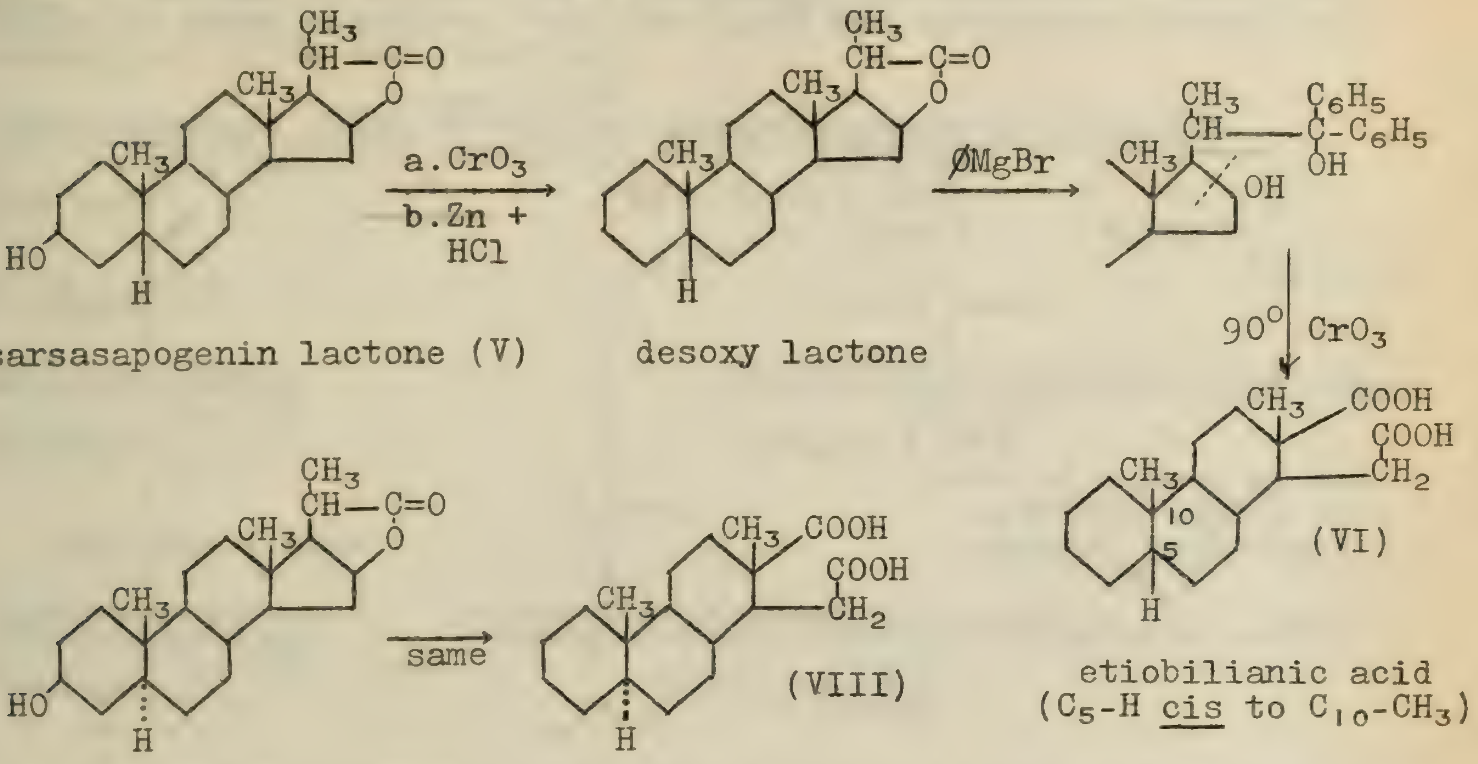
2) The hydroxyl group was shown to be in the usual C_3 position.

3) Oxidation of each sapogenin gave a lactone (III). Isolation of methylsuccinic acid (IV) from this oxidation indicated that the sapogenins have the same side chain skeleton as is present in cholesterol:



The structure of the lactones (III) was shown by Barbier-Wieland degradation. Thus, sarsasapogenin lactone (V) gave etiobilianic acid (VI), a known sterol degradation product. This degradation also established that rings A and B have the cis-decalin configuration;

i.e. the C_5-H is cis to the C_{10}-CH_3 group. Tigogenin lactone (VII) was degraded similarly to etioallobilianic acid (VIII), showing tigogenin to be a trans-decalin derivative, allo signifying a C_5-H trans to the C_{10}-CH_3.



sarsasapogenin lactone (V)

desoxy lactone

(VI)

etiobilianic acid
(C_5-H cis to C_{10}-CH_3)

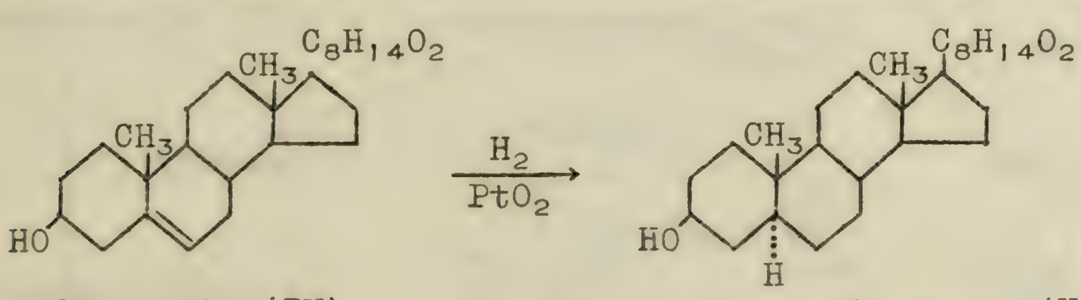
tigogenin lactone (VII)

(VIII)

etioallobilianic acid
(C_5-H trans to C_{10}-CH_3)

4) Smilagenin lactone was found to be identical with sarsasapogenin lactone (V), thus proving these sapogenins differ only in the side chain.

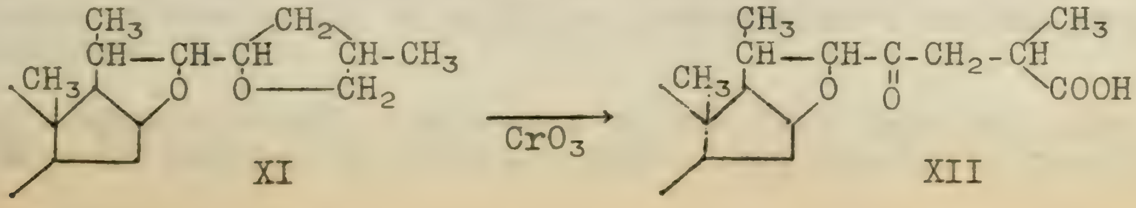
5) Diosgenin (IX), isolated in 1936 in Japan, was hydrogenated in neutral medium to give tigogenin (X). The C_5-C_6 position of the double bond was proved by Tsukamoto, using standard procedures.



diosgenin (IX)

tigogenin (X)

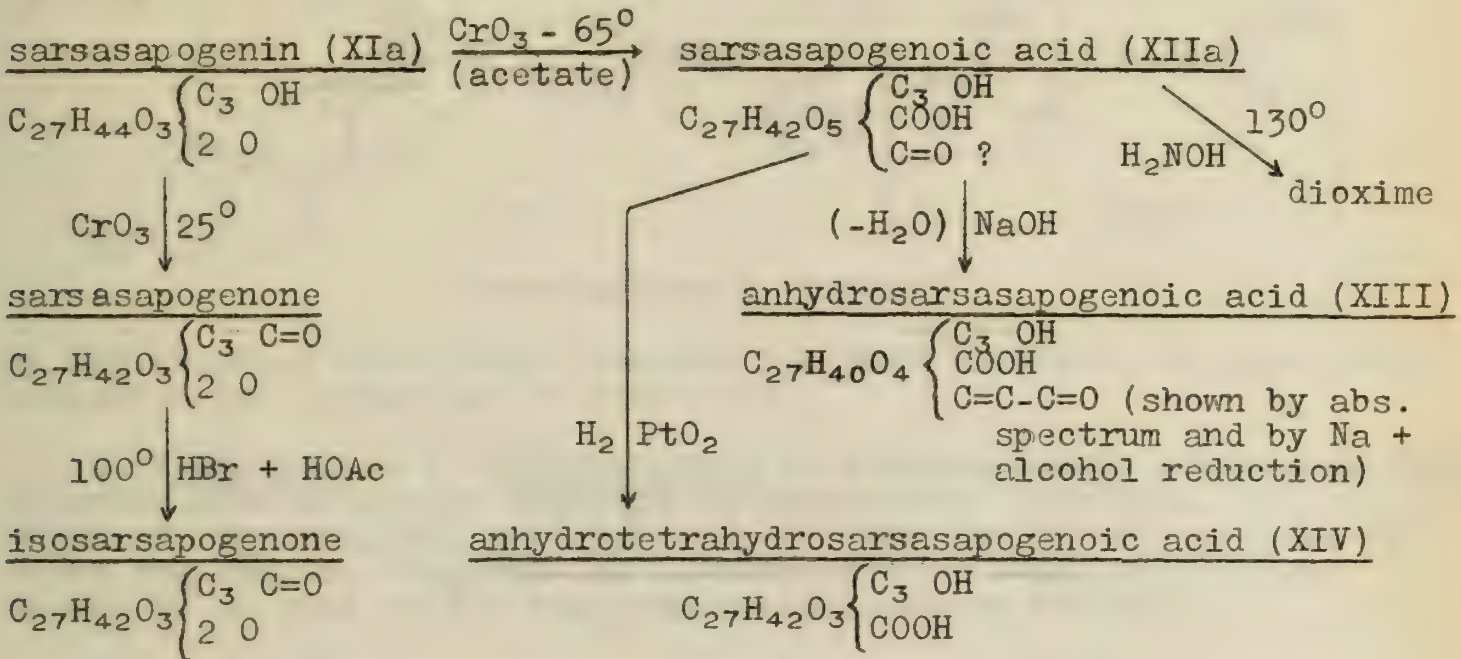
Thus, by the end of 1937, the structures of the sapogenins were complete except for the side chain. In 1935 Tschesche had tentatively suggested a difuran side chain (XI), and formulated the sapogenoic acid oxidation product ($C_{27}H_{42}O_5$) as a -keto acid (XII), although no carbonyl derivatives could be obtained.



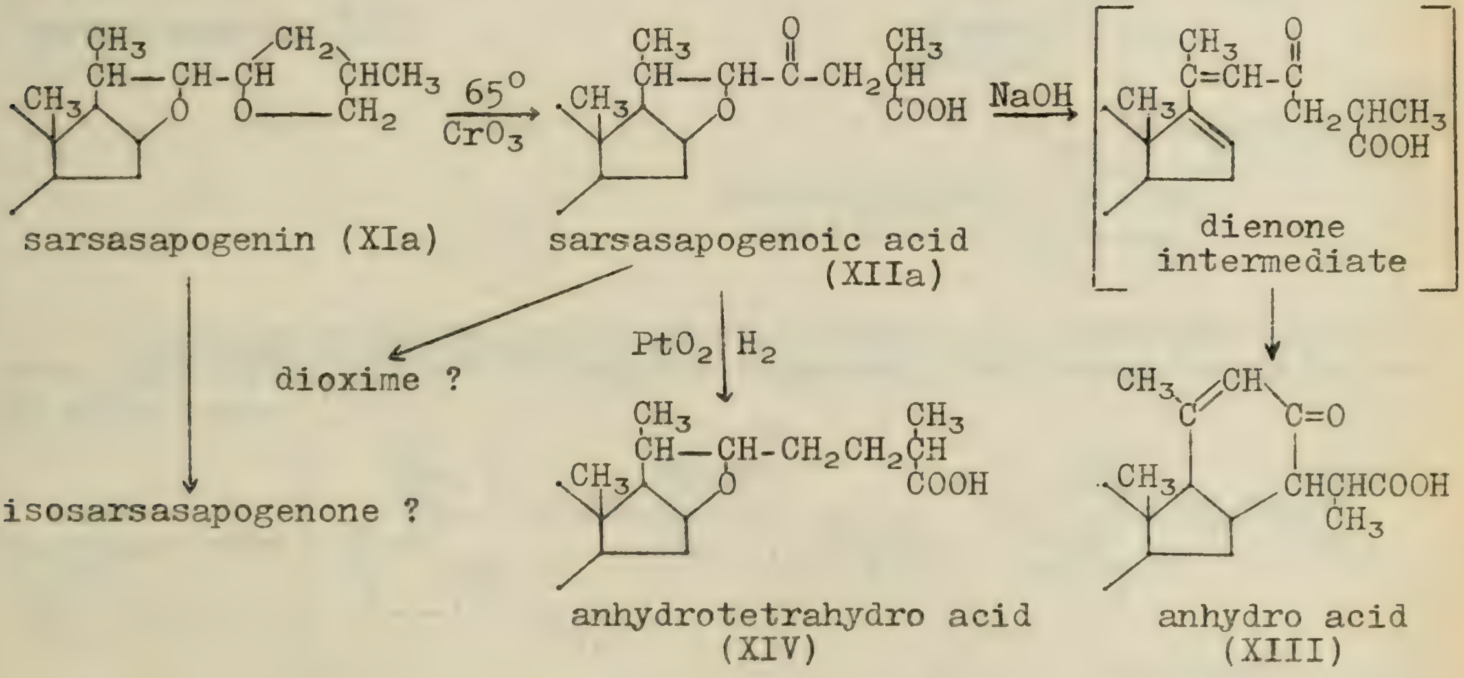
XI

XII

In 1938 Fieser attempted to solve the side chain problem. He was particularly interested in degrading the sapogenin to sex hormones, but his results were not encouraging. His most important reactions may be summarized as follows (throughout the abstract, "(acetate)" under an arrow signifies that the C_3-OH was acetylated before and hydrolyzed after the reaction):


sarsasapogenin (XIa)
$C_{27}H_{44}O_3$ C_3 OH, 2 O
CrO_3 - 65°
(acetate)
sarsasapogenoic acid (XIIa)
$C_{27}H_{42}O_5$ C_3 OH, COOH, C=O ?
130°
H_2NOH
dioxime
CrO_3 25°
sarsasapogenone
$C_{27}H_{42}O_3$ C_3 C=O, 2 O
$(-H_2O)$ NaOH
anhydrosarsasapogenoic acid (XIII)
$C_{27}H_{40}O_4$ C_3 OH, COOH, C=C-C=O (shown by abs. spectrum and by Na + alcohol reduction)
H_2 PtO_2
100° HBr + HOAc
isosarsapogenone
$C_{27}H_{42}O_3$ C_3 C=O, 2 O
anhydrotetrahydrosarsasapogenoic acid (XIV)
$C_{27}H_{42}O_3$ C_3 OH, COOH

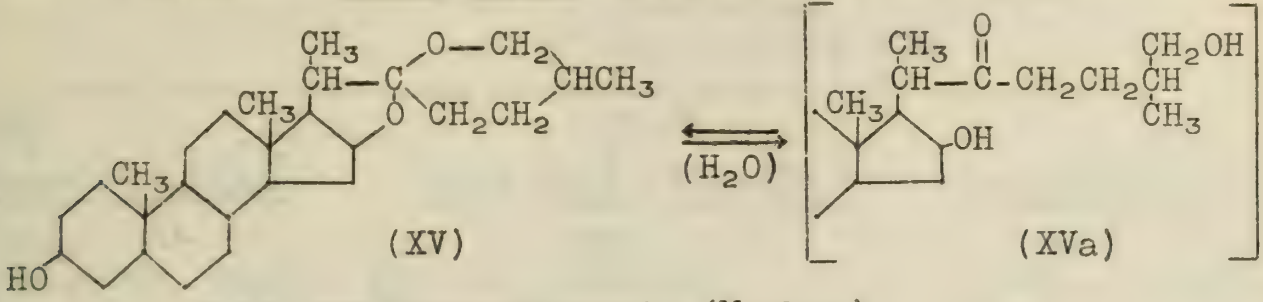
Fieser decided that his results could be explained by accepting Tschesche's structure for the side chain (XI) and the sapogenoic acids (XII), and he formulated the reactions of sarsasapogenoic acid as follows:



Fieser's principal contributions to the problem were: (1) Evidence of the reactivity and isomerization of the side chain in acid solution; (2) Conclusive evidence for a cyclic α,β-unsaturated ketone group in the anhydro acid (XIII).

Marker was particularly impressed by the fact that the side chain is unreactive in neutral or alkaline media, but unusually reactive in

acid solutions. He found that sarsasapogenin readily substituted bromine in the side chain and was oxidized by SeO_2. Although no products were identified from these reactions, they indicated a potential ketone, and the sensitivity to acid suggested a ketal. This interpretation, added to the evidence already available, prompted Marker to advance a spiro ketal formula (XV) for the side chain:

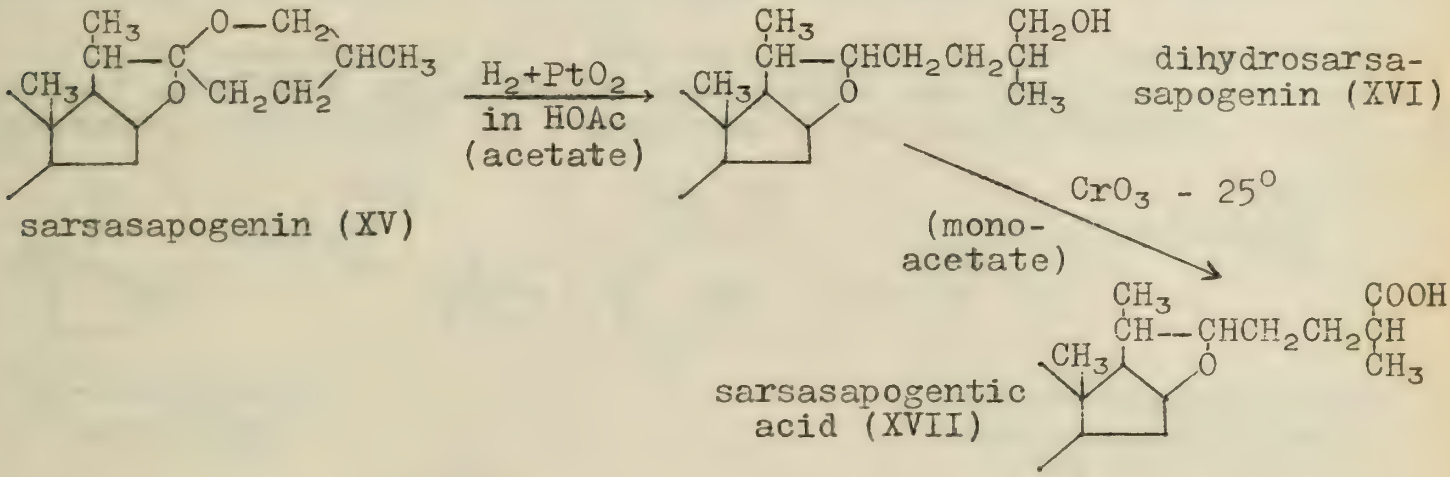


(XV) (XVa)

sarsasapogenin (Marker)

He has obtained convincing evidence for this structure by reduction, oxidation and isomerization reactions.

A. Reduction.— 1. Hydrogenation of sarsasapogenin acetate in acid solution gave a dihydro compound containing two hydroxyls, one of which was the original acetylated C_3-OH, and the other a primary OH, since the dihydro compound (as C_3-monoacetate) could be oxidized easily to an acid called sarsasapogentic acid by Marker:

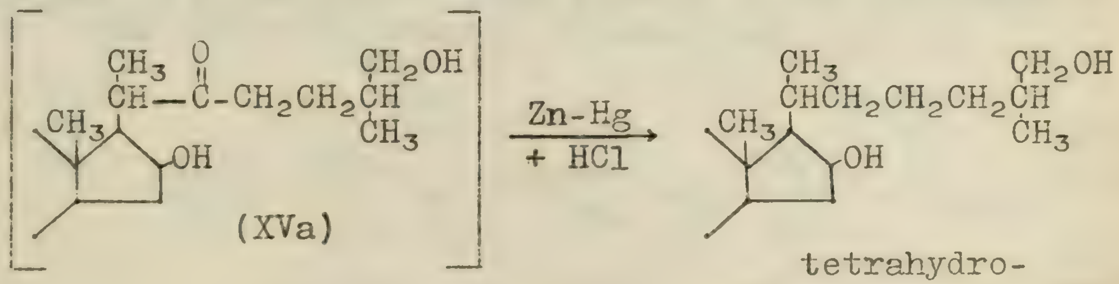


sarsasapogenin (XV)

dihydrosarsasapogenin (XVI)

sarsasapogentic acid (XVII)

2. Clemmensen reduction of sarsasapogenin, in accordance with the keto form (XVa), gave a tetrahydro compound, the ketone being reduced to methylene.



sarsasapogenin (XV)

(XVa)

tetrahydrosarsasapogenin (XVIII)

B. Oxidation.— In addition to sarsasapogenin lactone (V), whose structure had been well-established, and sarsasapogenoic acid, to which Marker assigned a γ-diketo structure (XX), Marker also isolated a keto acid (XIX) from the oxidation of sarsasapogenin acetate with CrO_3 at 60° in acid solution.

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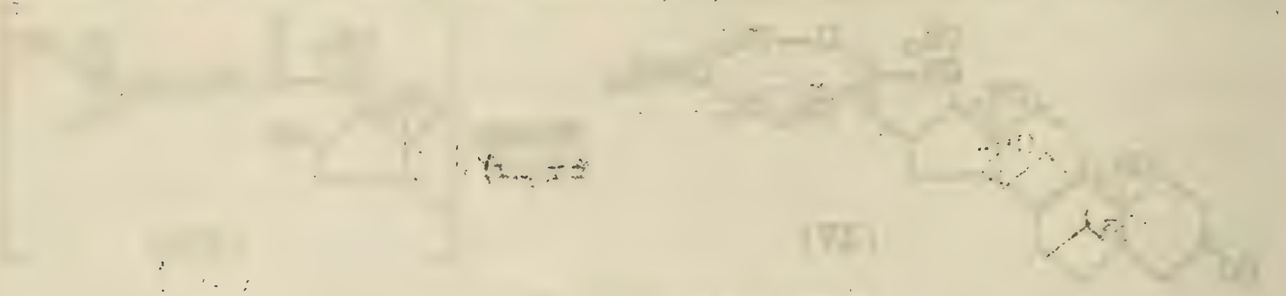

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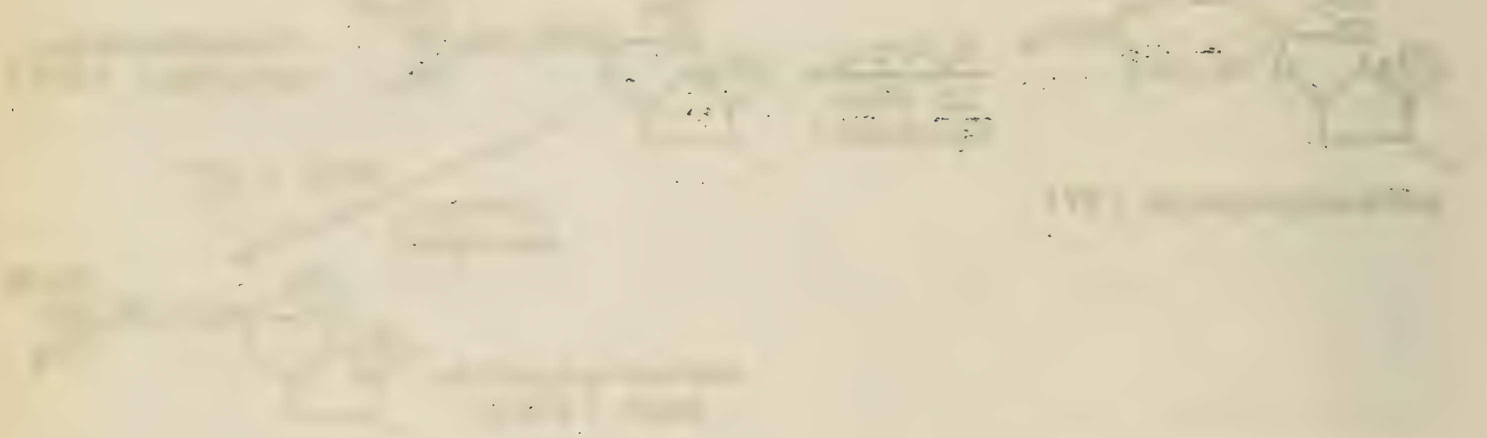

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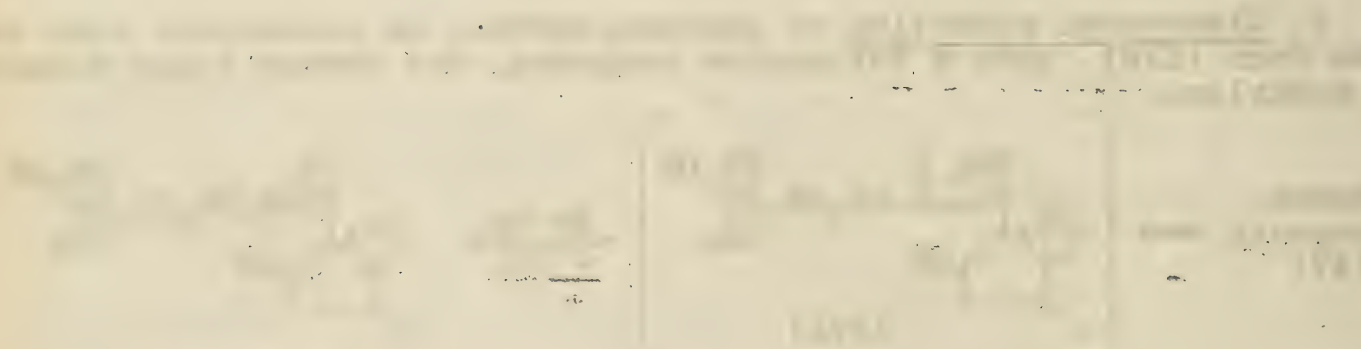

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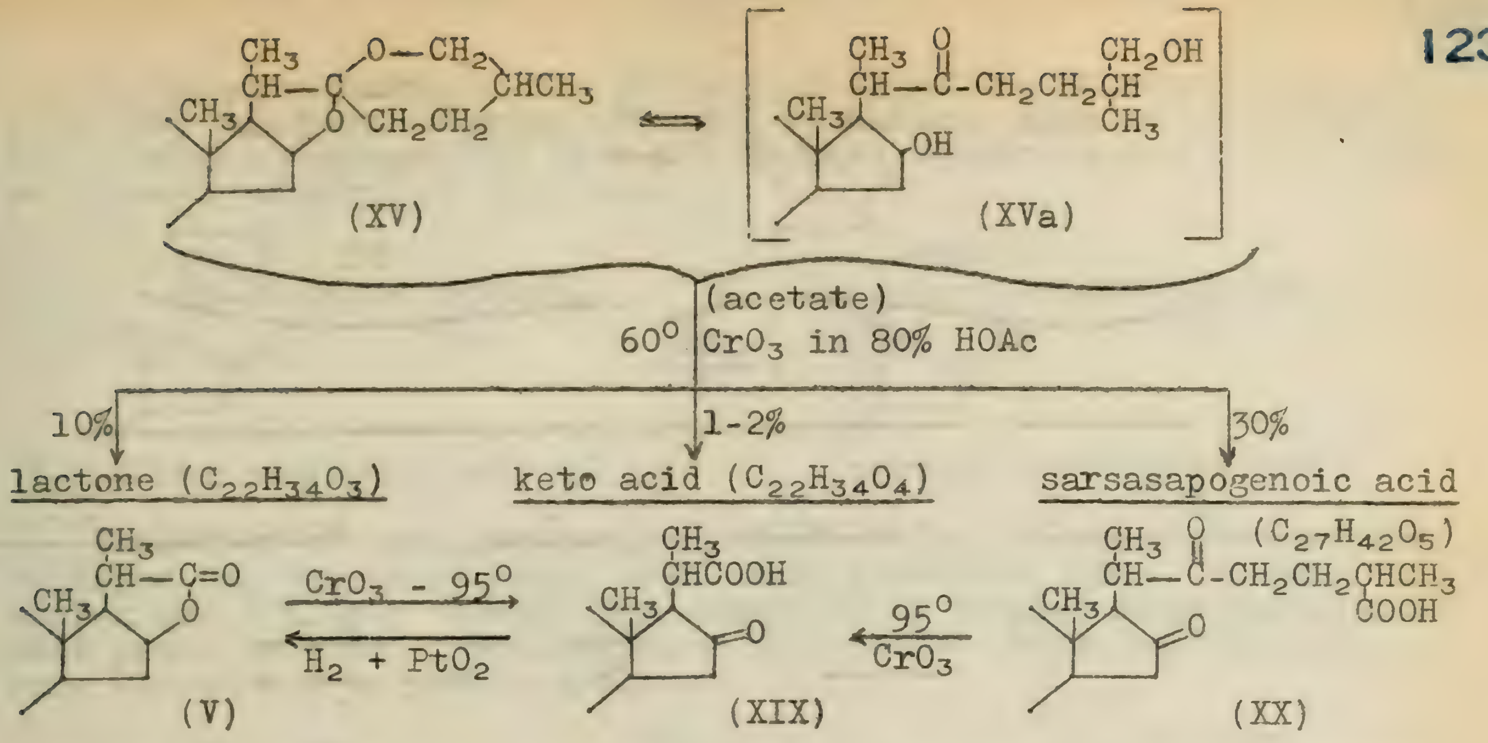
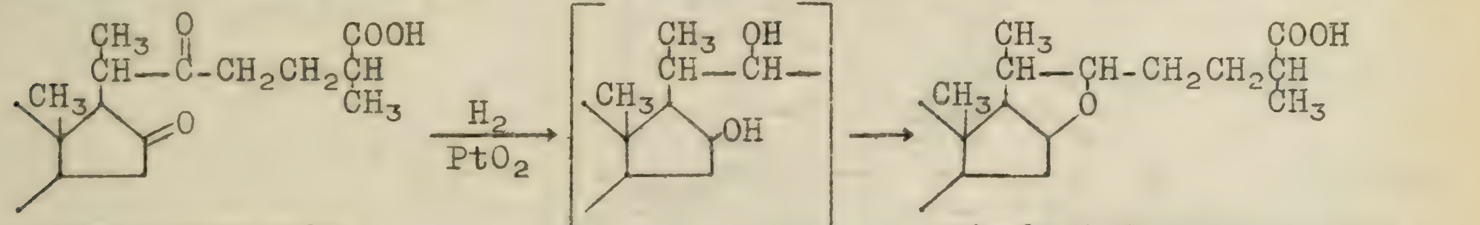


The γ-diketone structure which Marker assigned to sarsasapogenoic acid (XX) was strongly supported by the following reactions which were originally carried out by Fieser:

1) Sarsasapogenoic acid (XX) forms a dioxime, although it is necessary to heat the acid with H_2NOH in a sealed tube at 130°.

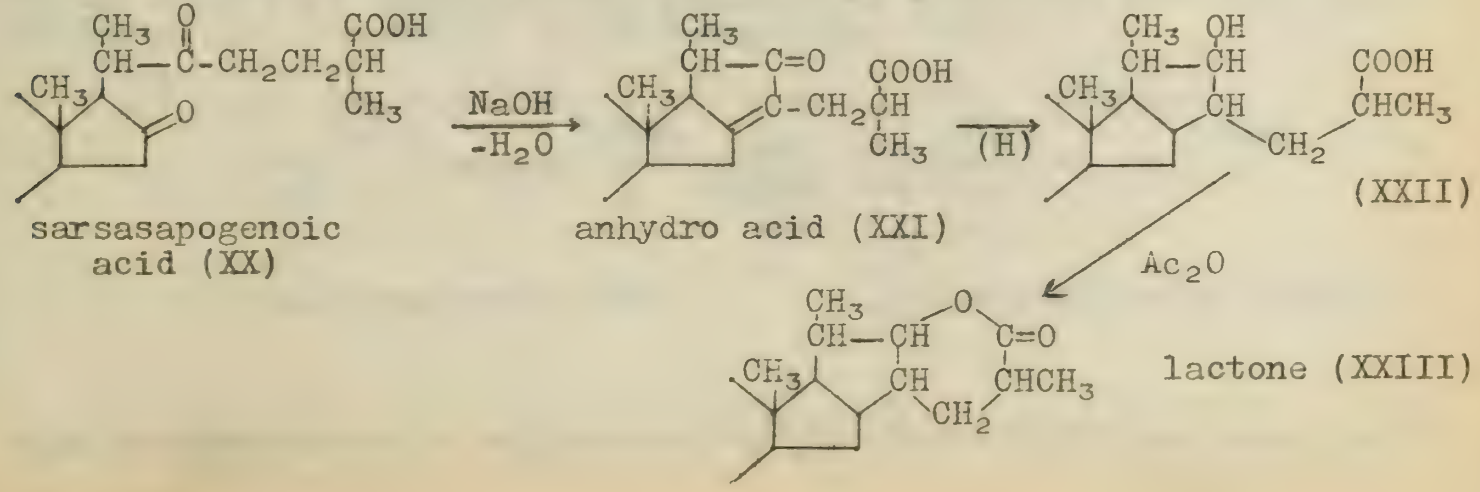
2) Sarsasapogenoic acid (XX) was reduced to the "anhydrotetrahydro" acid (XIV) which Marker then proved was identical with sarsasapogentic acid (XVII) by comparison of various derivatives (cf. p. 4).



sarsasapogenoic acid (XX)

anhydrotetrahydro acid (sarsasapogentic acid) (XIV and XVII)

3) Reaction of a γ-diketone with alkali should give a cyclic α,β-unsaturated ketone, which was shown by Fieser to be present in anhydrosarsasapogenoic acid (XXI). This type of aldol condensation is more plausible than Fieser's dienone intermediate (p. 3).

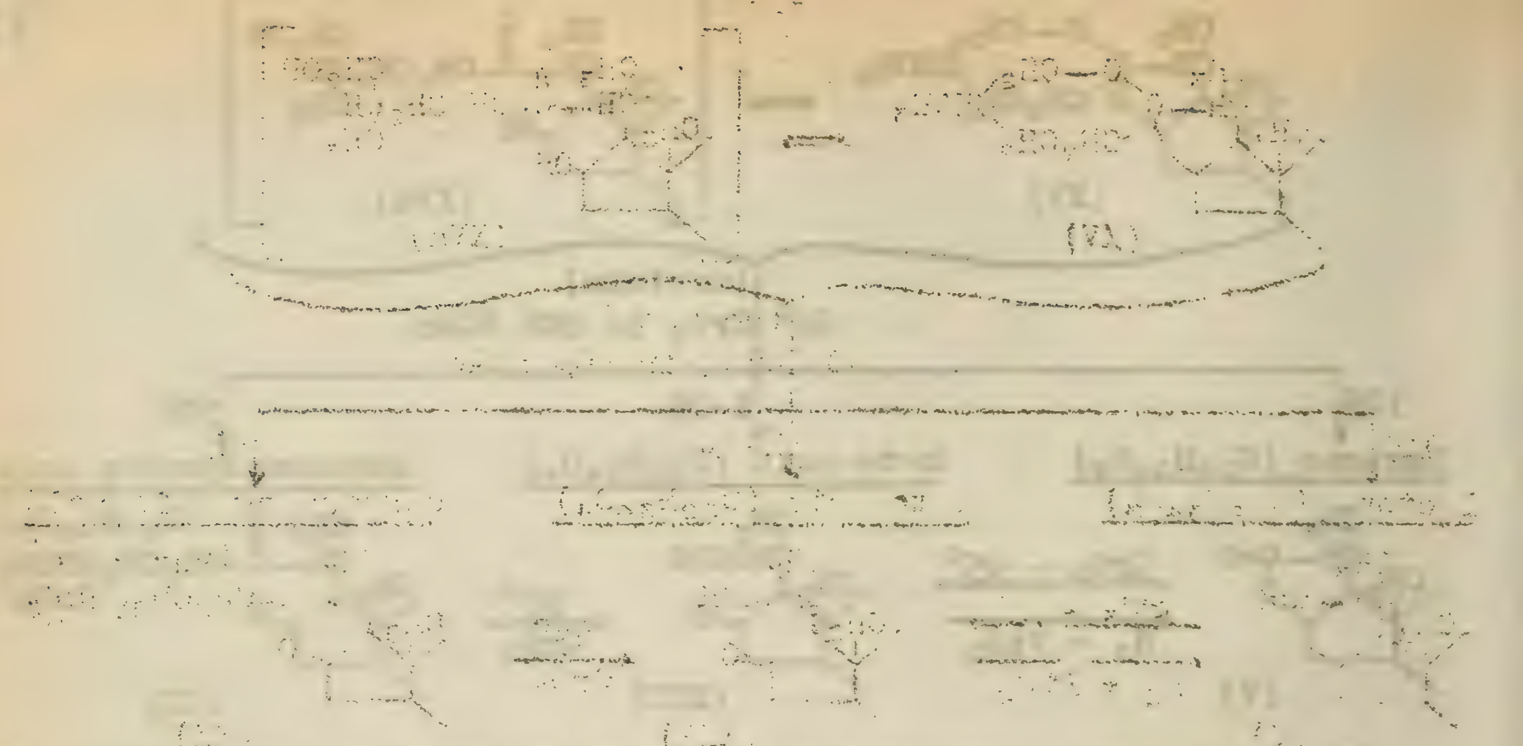


sarsasapogenoic acid (XX)

anhydro acid (XXI)

(XXII)

lactone (XXIII)



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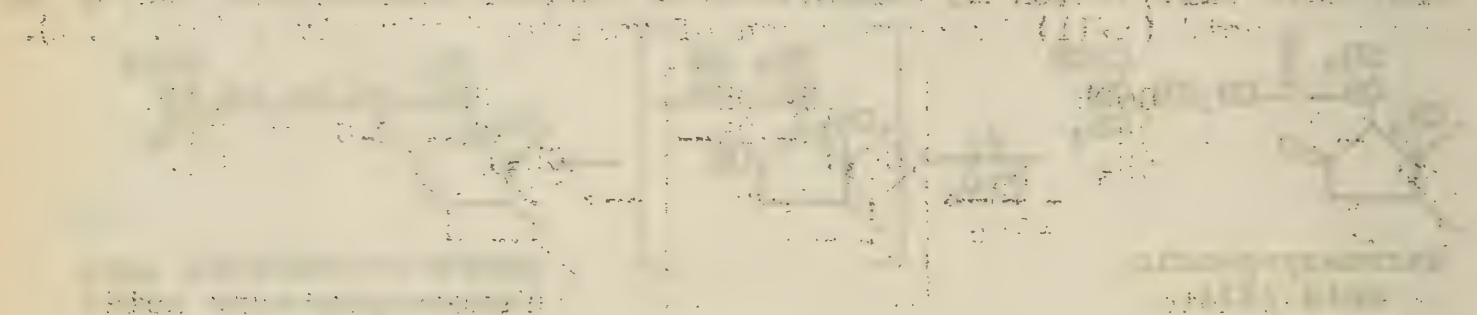

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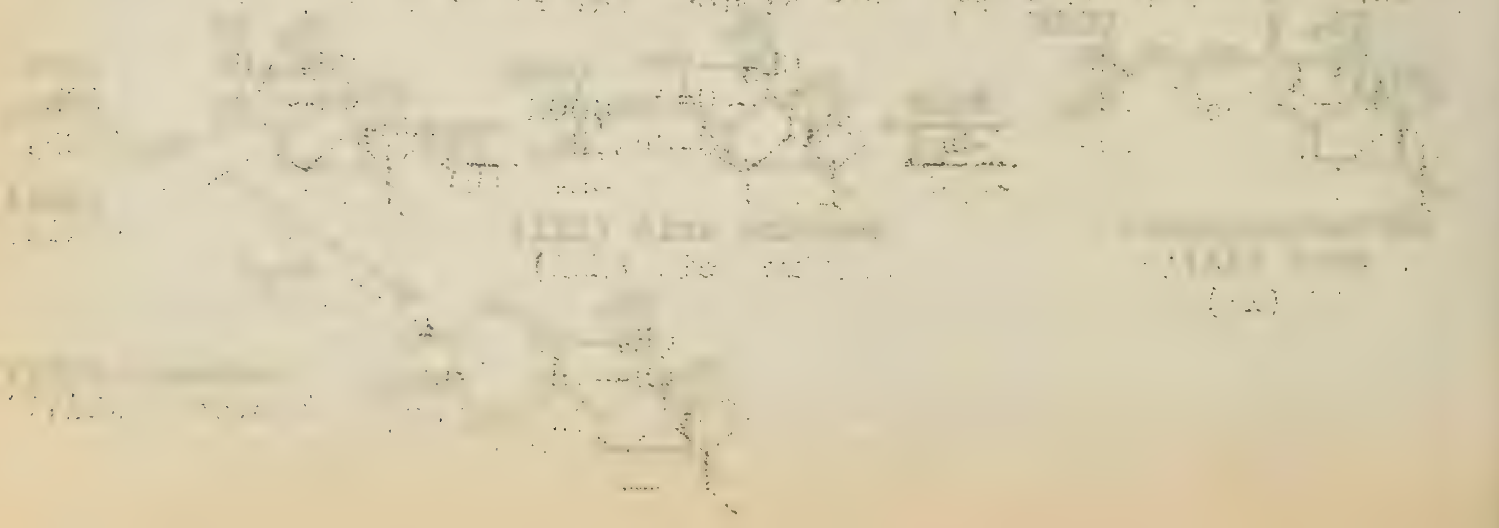
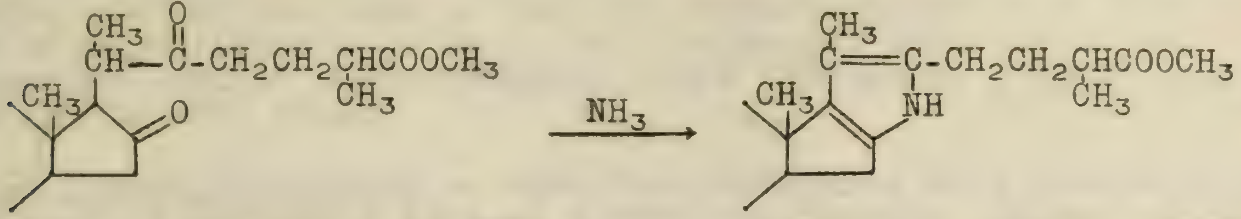
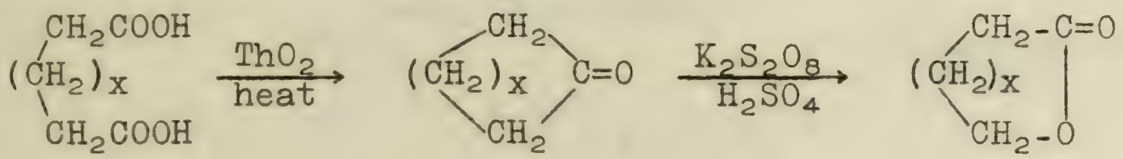


Further evidence for the γ-diketone structure of sarsasapogenoic acid (XX) has been recently obtained by Noller. The methyl ester of the acid reacted smoothly with NH_3 to give a pyrrole derivative (XXIV) as shown by absorption spectrum.

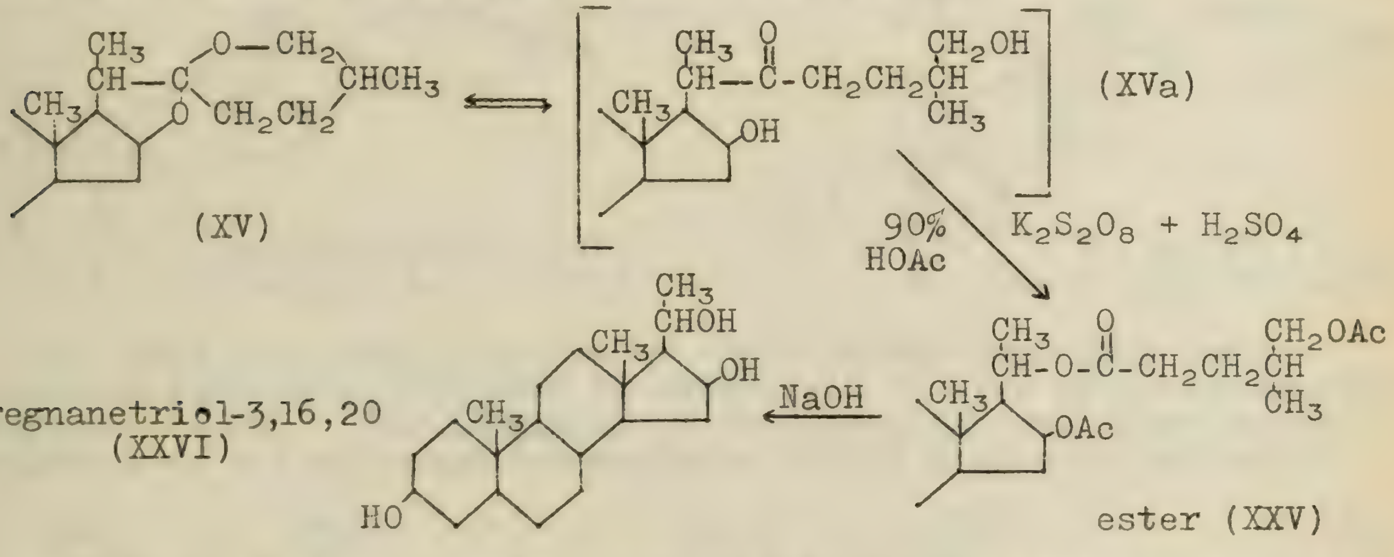


sarsasapogenoic acid (XX) pyrrole derivative (XXIV)

Oxidation of sarsasapogenin with persulfuric acid also provided evidence for the spiro ketal side chain structure (XV). In 1899 Baeyer and Villiger showed that oxidation of ketones with persulfuric acid gives lactones. Ruzicka used this method for preparing large ring lactones from cyclic ketones:

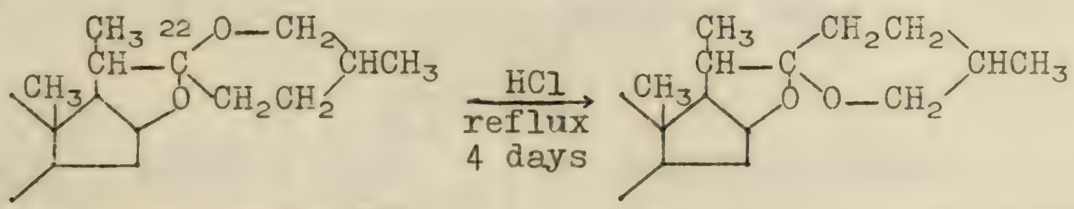


Sarsasapogenin was oxidized with this reagent and the product hydrolyzed with alkali to give a pregnanetriol (XXVI):

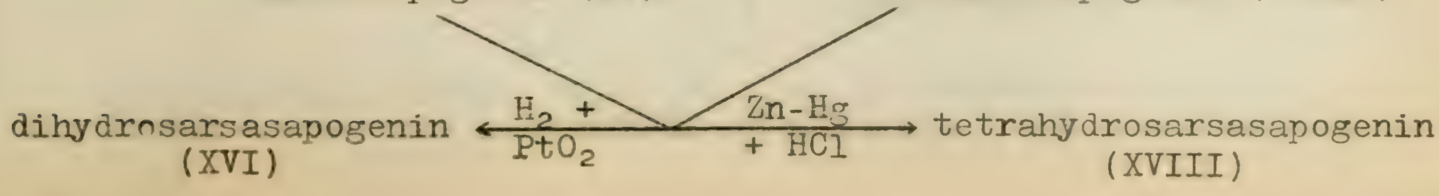


pregnanetriol-3,16,20 (XXVI) ester (XXV)

C. Isomerizations.— Refluxing sarsasapogenin (XV) for 4 days with HCl in ethanol caused isomerization at the spiro carbon (C_{22}) as shown by the fact that isosarsasapogenin (XXVII) gives the same reduction products (XVI and XVIII) as sarsasapogenin (XV):



sarsasapogenin (XV) isosarsasapogenin (XXVII)

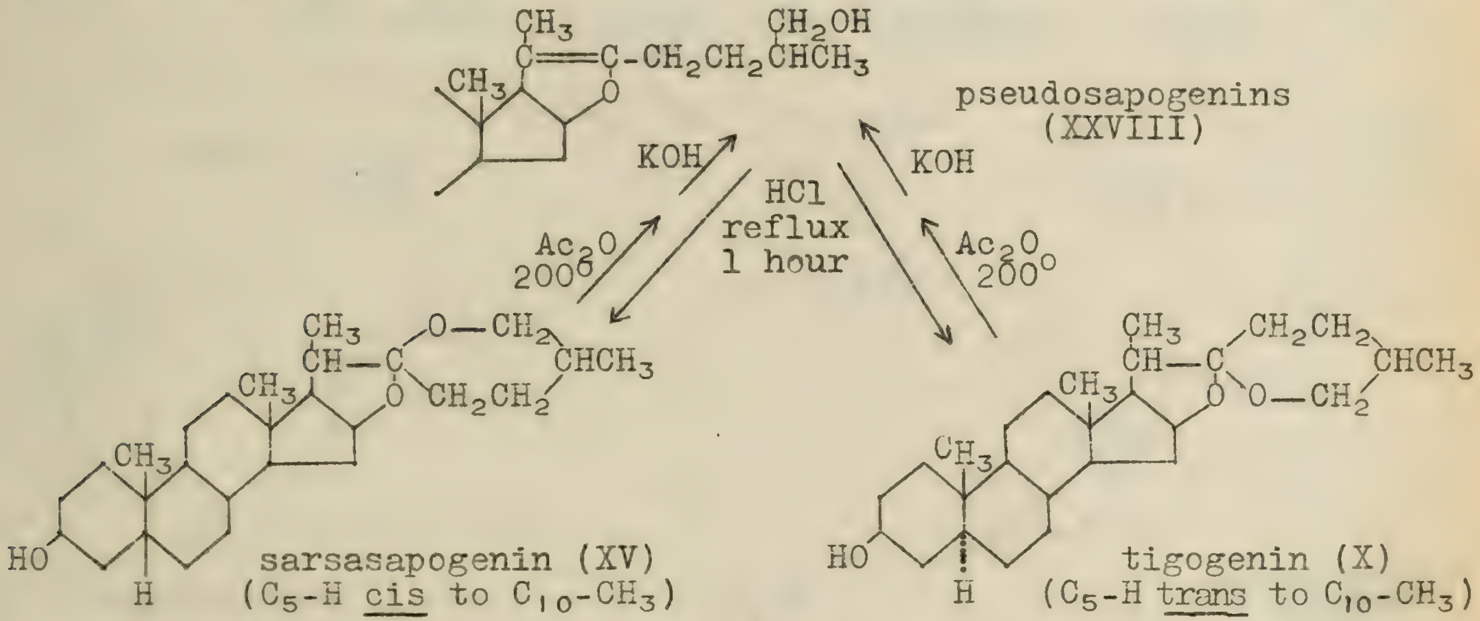


dihydrosarsasapogenin (XVI) tetrahydrosarsasapogenin (XVIII)

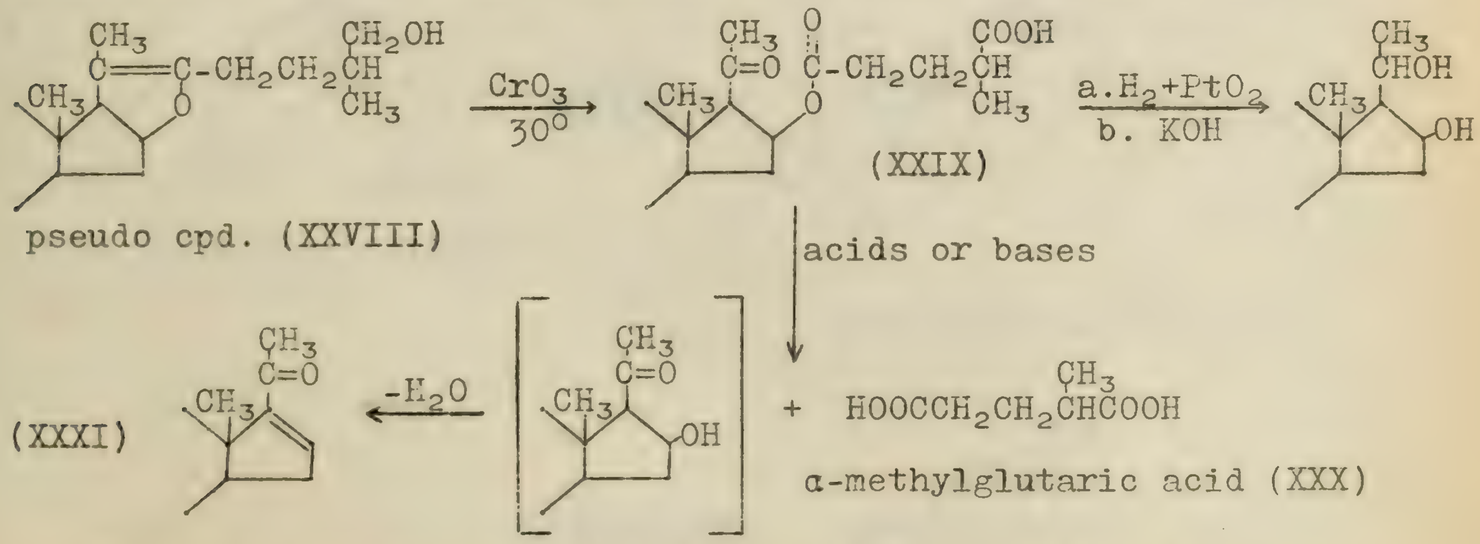
A comparison of various derivatives proved isosarsasapogenin (XXVII) to be identical with smilagenin (see p. 2).

Marker found that the side chain of all the other sapogenins reacted exactly the same as that in sarsasapogenin, with the exception of isomerization by HCl. This suggested that all of the sapogenins, except sarsasapogenin, have the stable ("iso") configuration in the side chain.

D. Pseudo Sapogenins.— When the sapogenins were heated at 200° with Ac_2O, a different type of isomer was formed. Marker called these isomers pseudosapogenins (XXVIII). The reaction was reversed by refluxing the pseudo compounds with HCl for 1 hour; although both side chain isomers (XV + XXVII) would be expected from this reverse isomerization, one form was obtained almost quantitatively and its side chain configuration was determined by the configuration at C_5:



The most important reaction of these pseudo compounds involved oxidation with CrO_3, followed by hydrolysis to give Δ^{16}-pregnenone-20 compounds (XXXI). The mechanism of this reaction was shown by the isolation of a keto ester intermediate (XXIX) from mild oxidation:



This reaction proved to be the clue to conversion of the sapogenins to the sex hormones in good yields. For this purpose,

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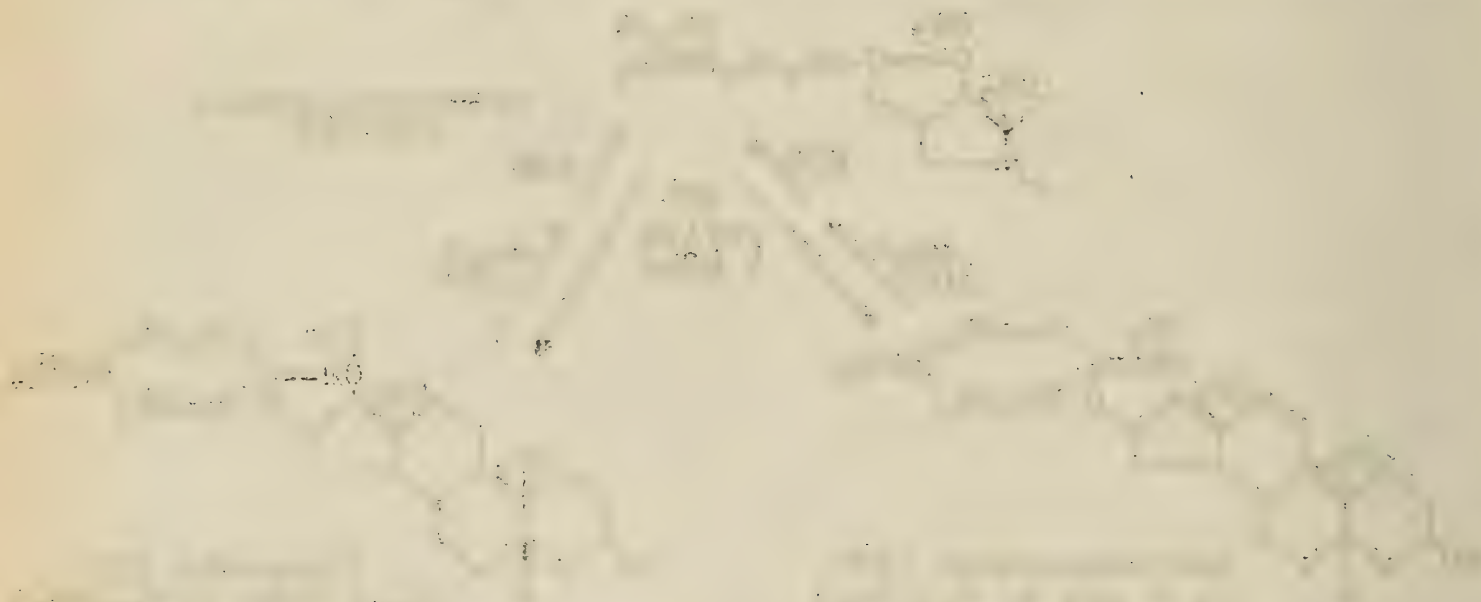

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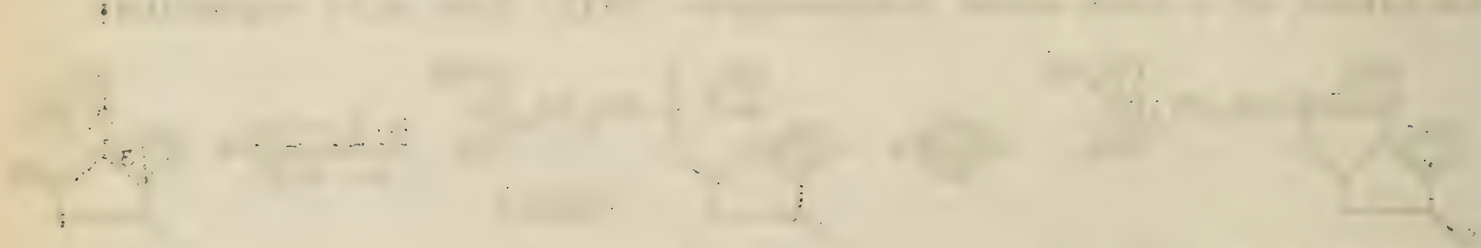

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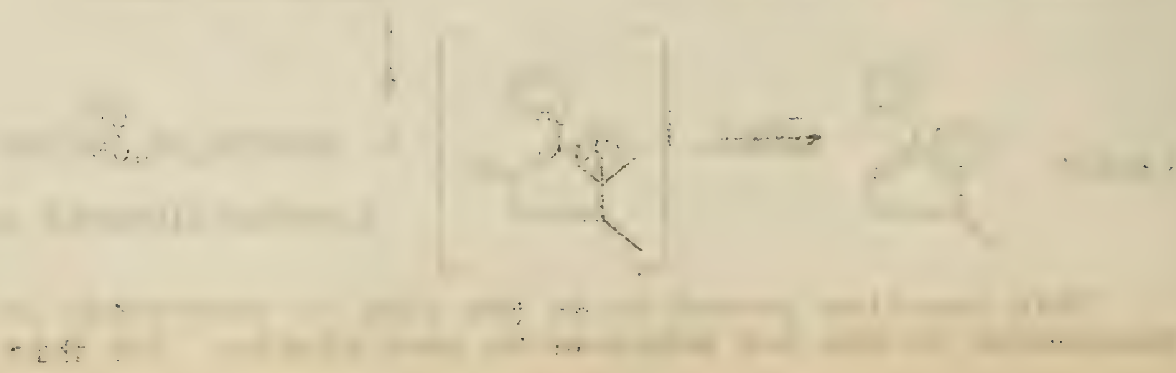

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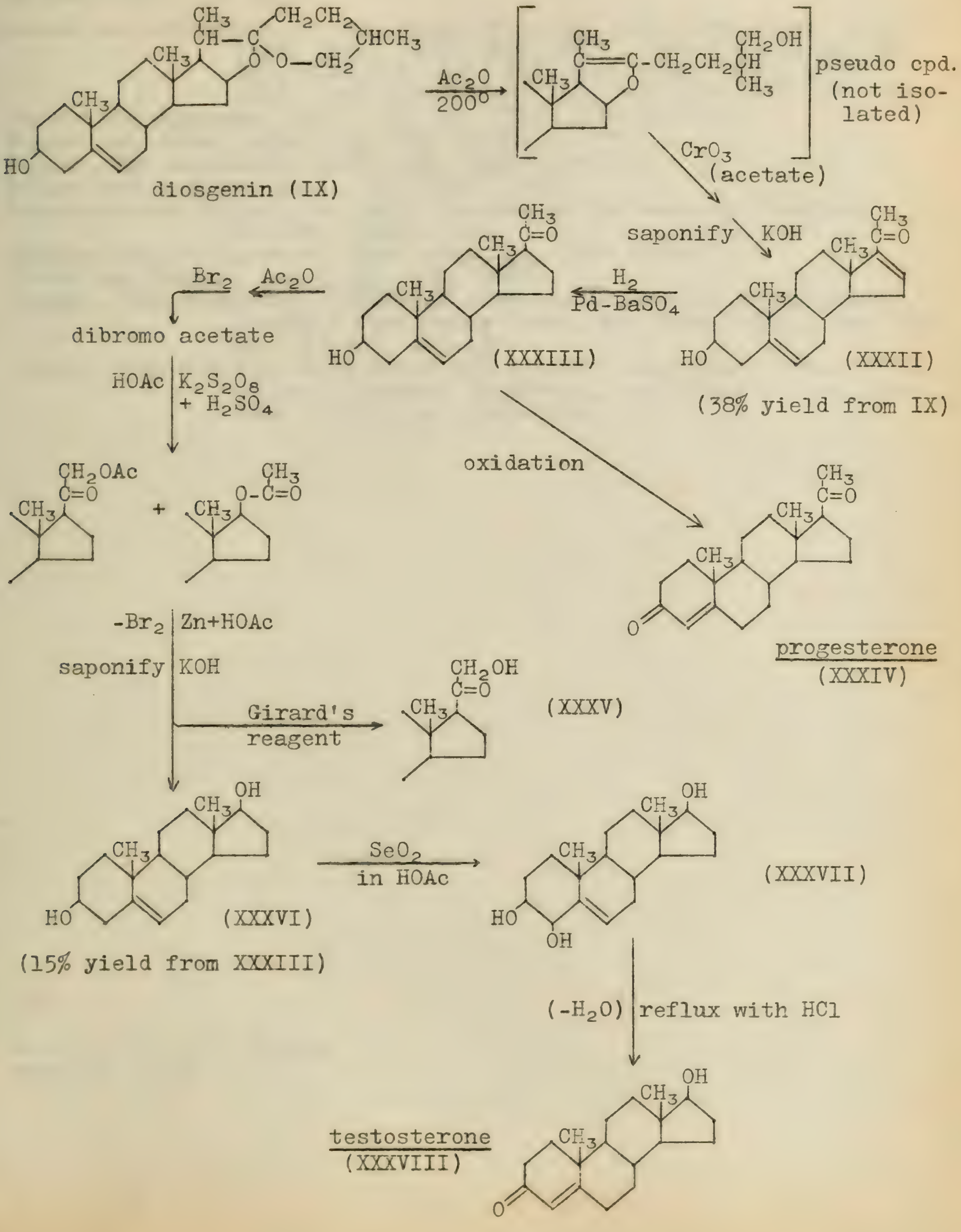
diosgenin (IX) was used since there was already a double bond in the nucleus. It was found unnecessary to isolate the pseudo compound, which could be oxidized directly to the ketol XXXII without protecting the double bond.



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Marker and coworkers, J. Am. Chem. Soc., 61, 846, 1284, 1285, 1291, 1516, 1921, 2072, 2722, 3477, 3592 (1939); 62, 76, 222, 518, 521, 525, 647, 900, 1162, 2525, 2532, 2543, 3349 (1940); 63, 763, 767, 774, 777, 779 (1941).
Fieser and Jacobsen, ibid., 60, 28, 2753, 2761 (1938).
Fieser and Jones, ibid., 61, 532 (1939).
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Reported by E. H. Riddle
April 30, 1941

METALLOPORPHYRIN COMPLEXES

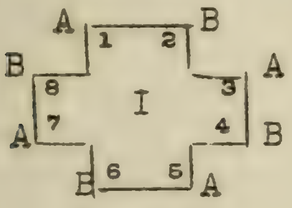
Hans Fischer et al - Munich Zurich
W. M. Clark et al - Johns Hopkins School of Medicine

In this discussion an attempt will be made to review briefly the principal methods of porphyrin synthesis, the preparation of metalloporphyrins, and some of the properties of the nitrogenous base complexes of metalloporphyrins.

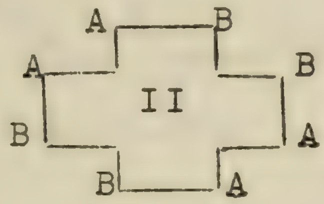
The biochemical significance of metalloporphyrin complexes needs only brief mention. Hemoglobin is a ferrous-porphyringlobin complex; the cytochromes (important tissue oxidation catalysts) are ferric-porphyrin-protein complexes; the H_2O_2 -destroying enzyme, catalase, is a ferric-porphyrin-protein complex; chlorophyll is a magnesium-porphyrin (protein?) complex; and the list may be expanded to include several other systems. The above incomplete list will serve to illustrate the chemical versatility of the iron-porphyrin group in particular.

I. Porphyrin Synthesis

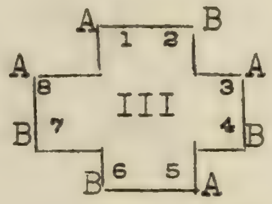
By employing properly beta-substituted pyrroles, a great variety of substituted porphyrins can be prepared. If we deal only with pyrroles whose beta positions are substituted with an A and a B group, we arrive at four possible structural arrangements, as illustrated below:



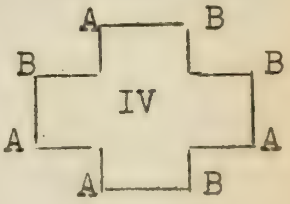
Type I



Type II



Type III

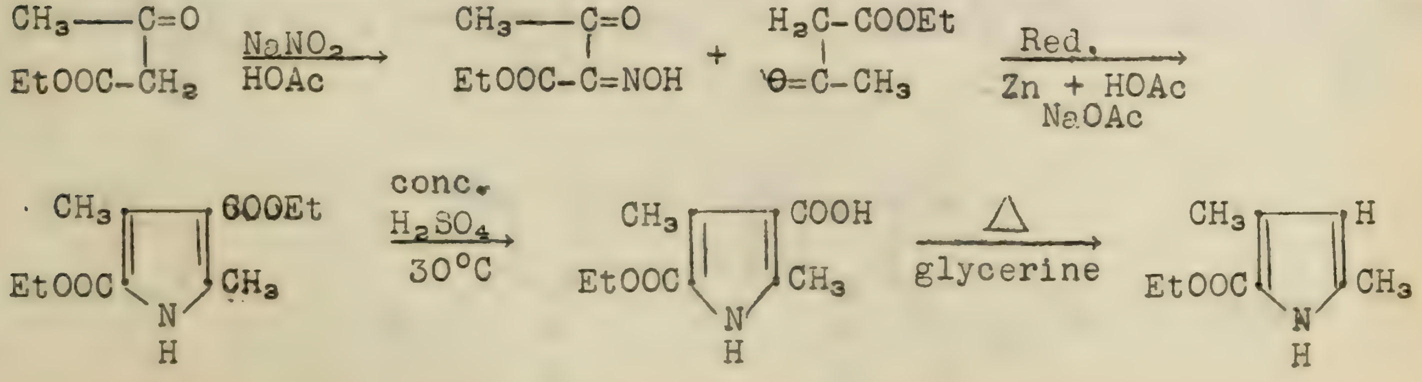


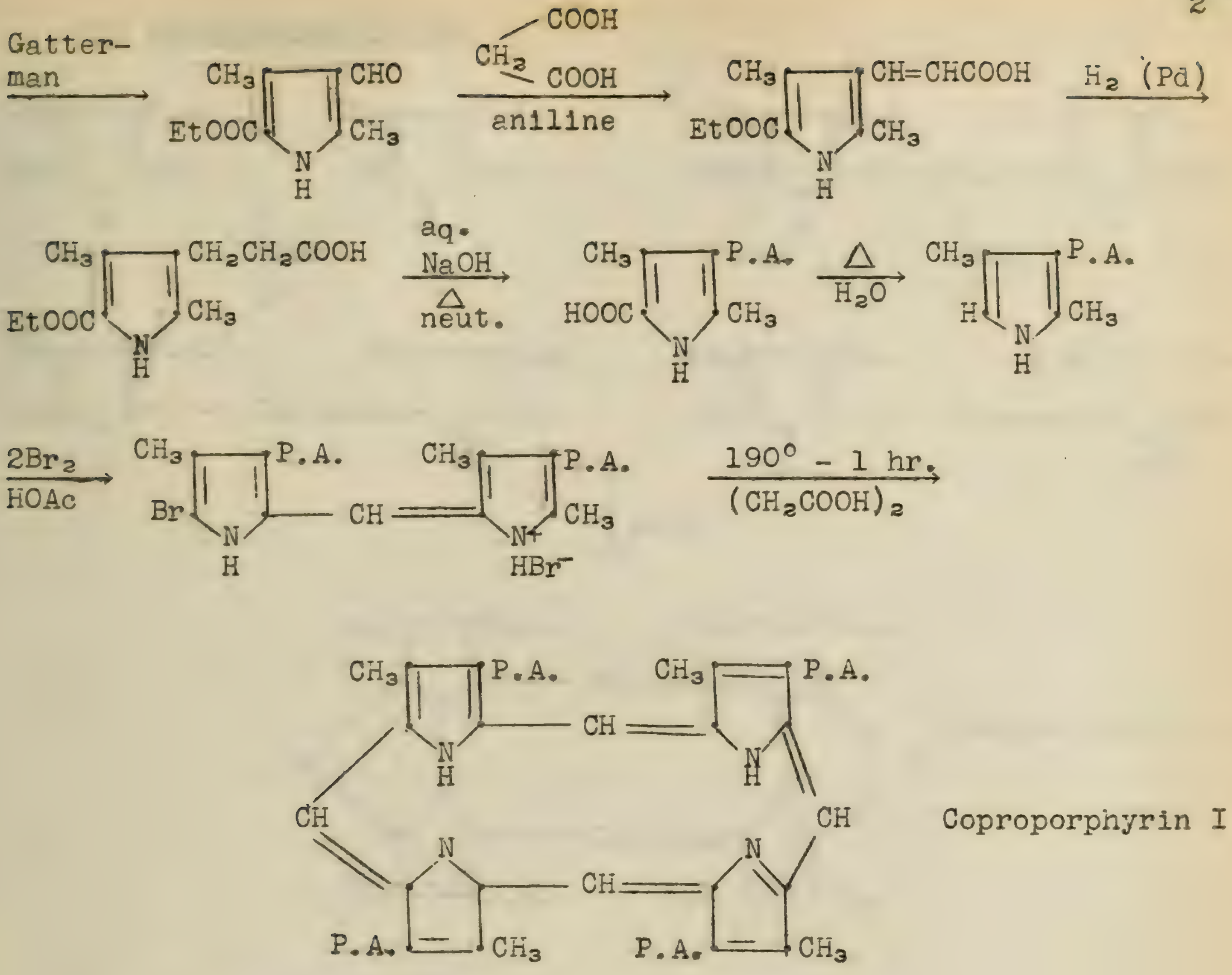
Type IV

It is interesting to mention what Hans Fischer has called the "dualism of the porphyrins"; only Types III and I (the latter apparently a by-product and present in far less quantity) have been isolated from natural sources.

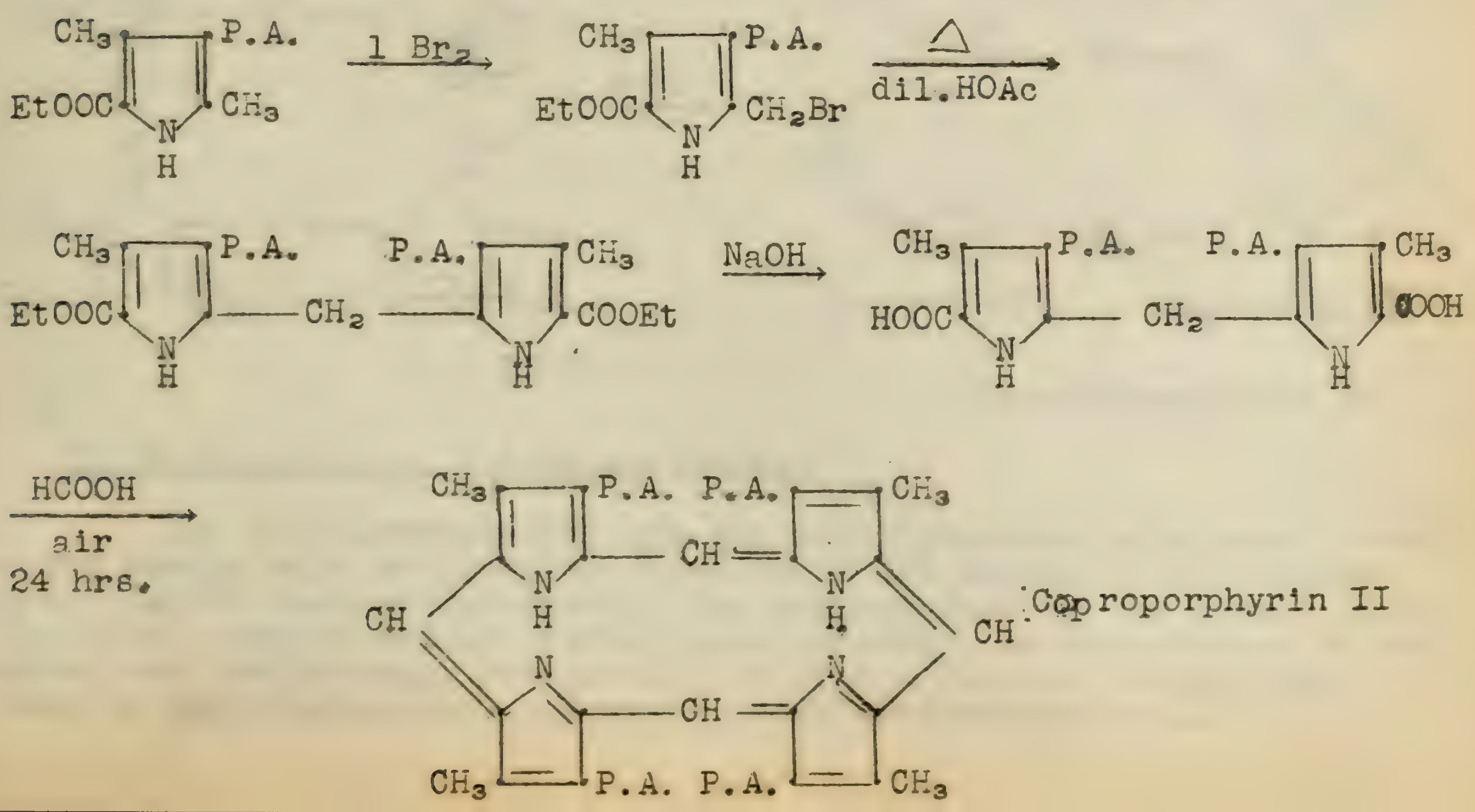
The main synthetic methods will be illustrated by several examples:

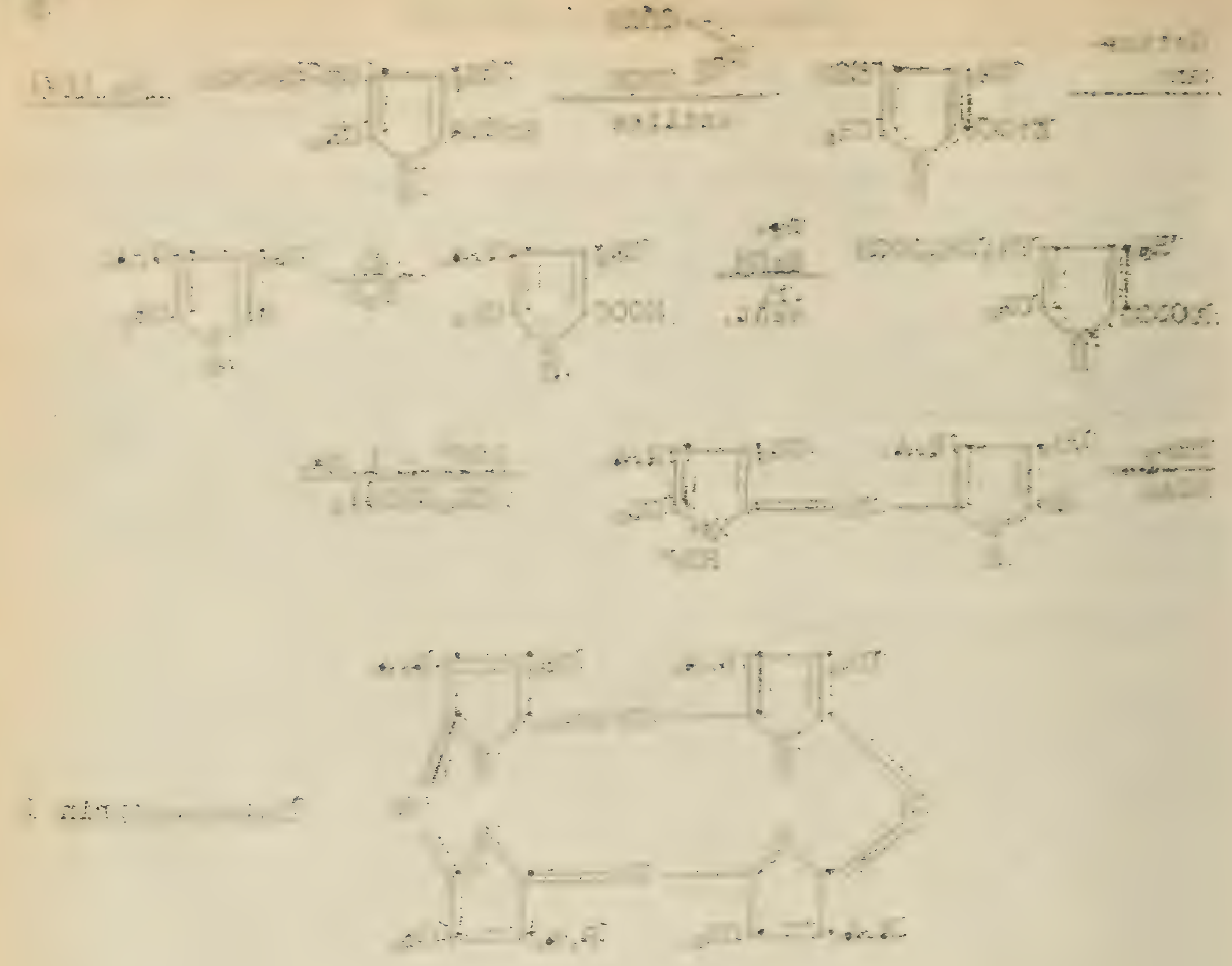
(1) Coproporphyrin I





(2) Coproporphyrin II





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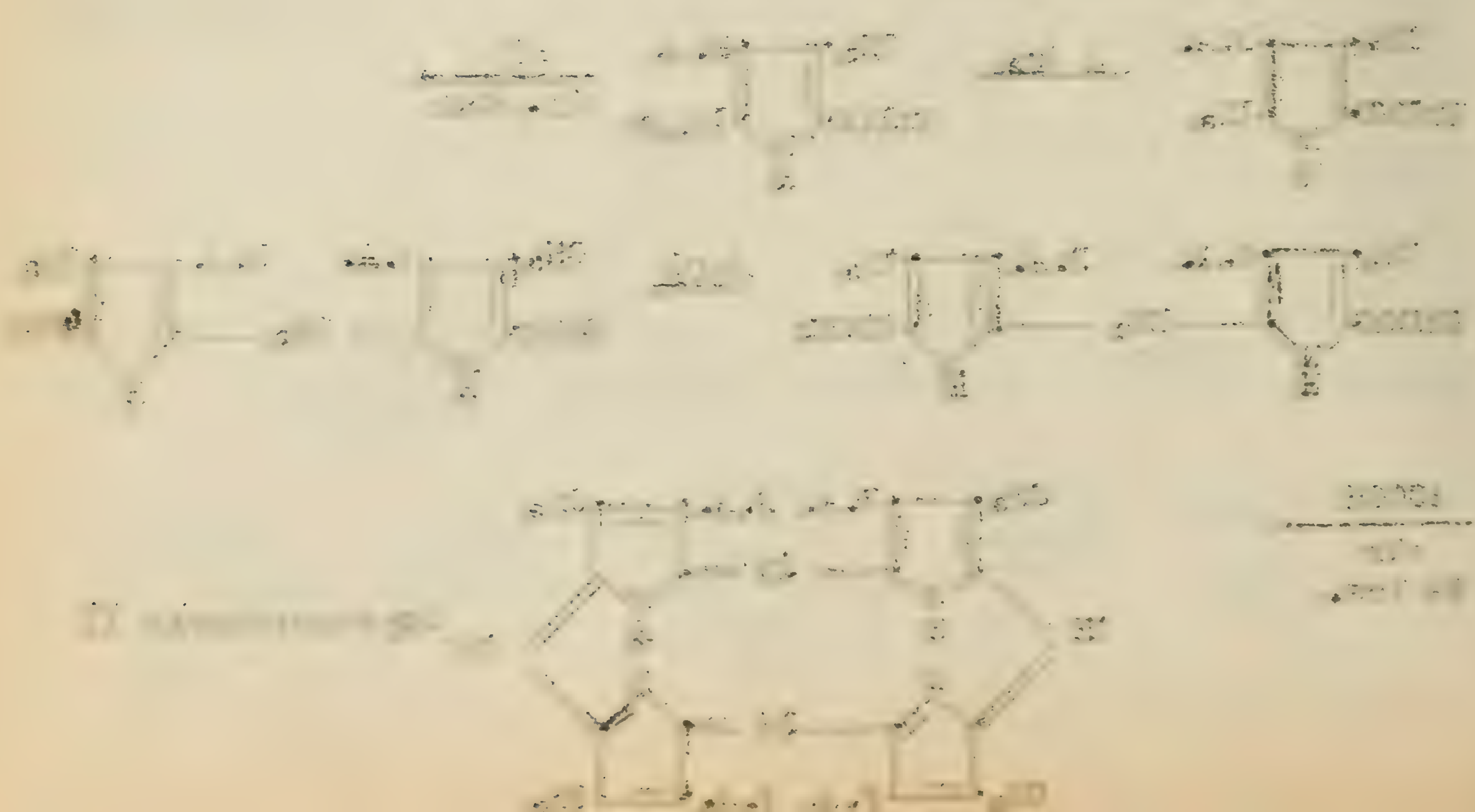
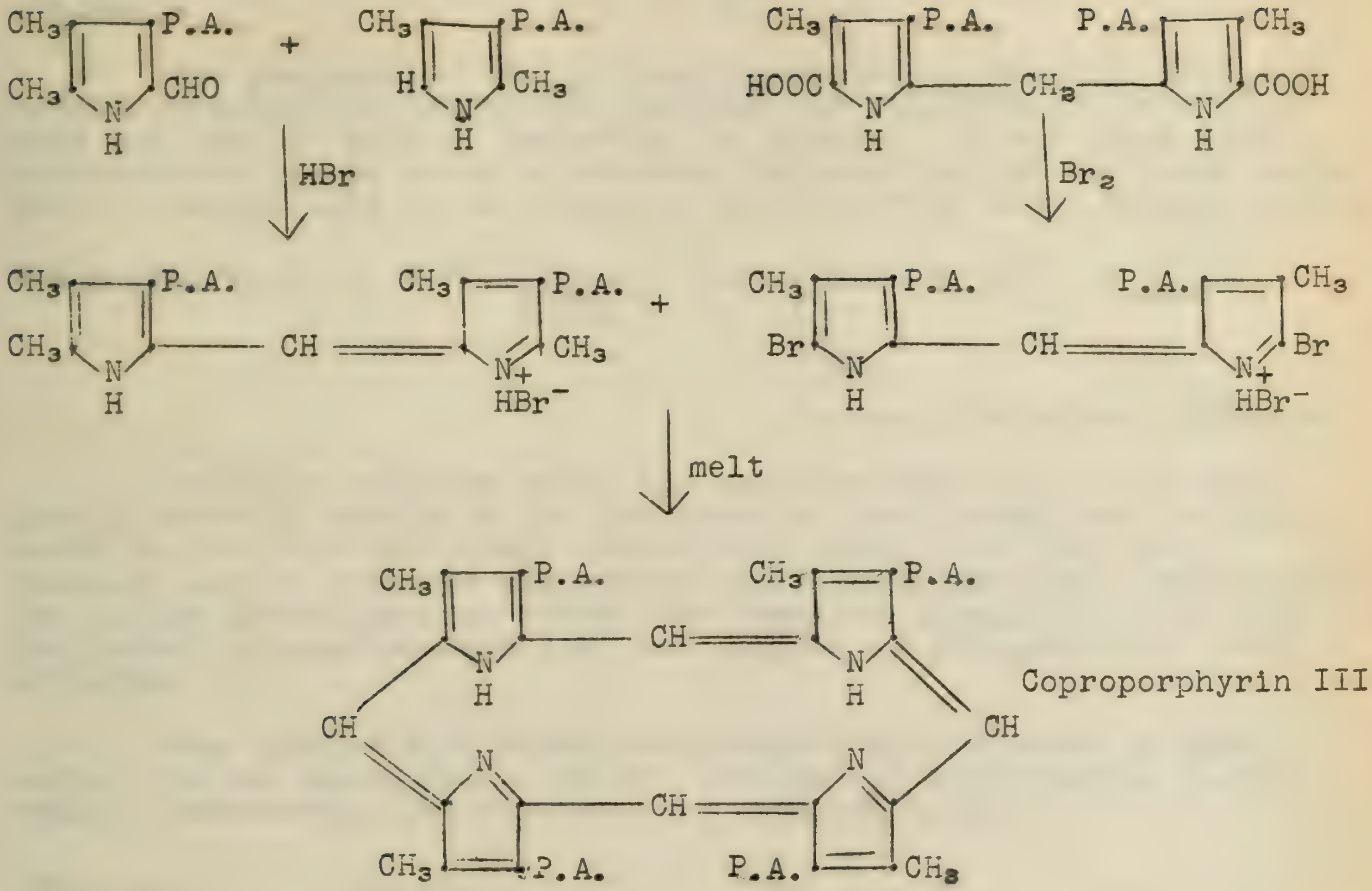
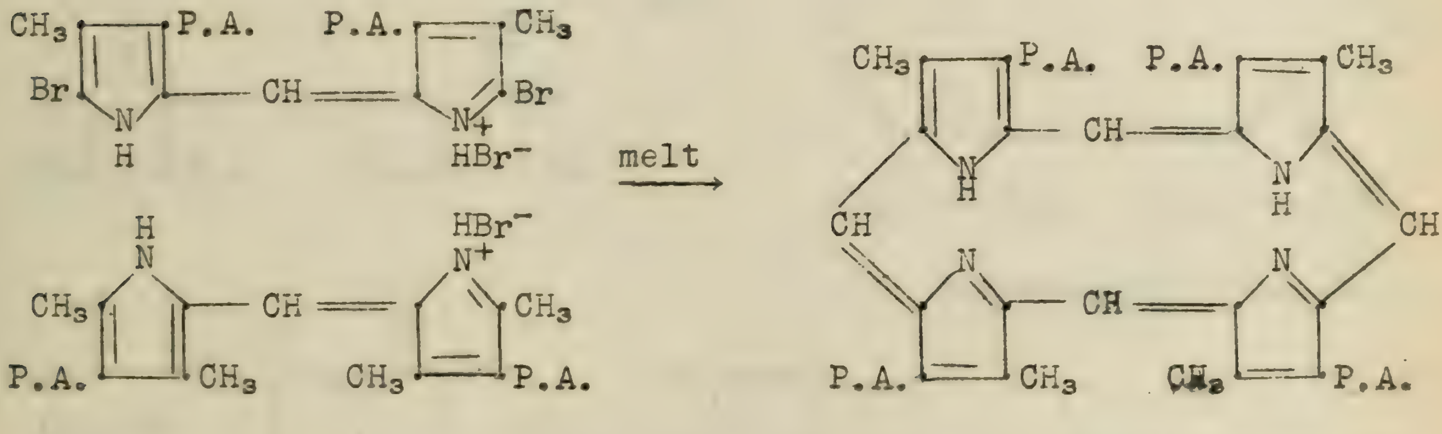


(3) Coproporphyrin III



Coproporphyrin III

(4) Coproporphyrin IV



Coproporporphyrin IV

II. Preparation of Metalloporphyrins

The metalloporphyrins are generally prepared with great ease. A hot acetic acid or pyridine solution of the porphyrin is treated with a metal acetate (preferably the reduced form of the metal), and the metal complex either crystallizes directly, or the solvent is removed and the material recrystallized from a solvent combination, such as pyridine-acetic acid-water or chloroform-methanol.

By modifications of this technique and by several other methods, the following metalloporphyrins have been prepared and characterized: Fe, Co, Mn, Ni, Cu, Mg, Sn, Zn, K, Ag, and several others.

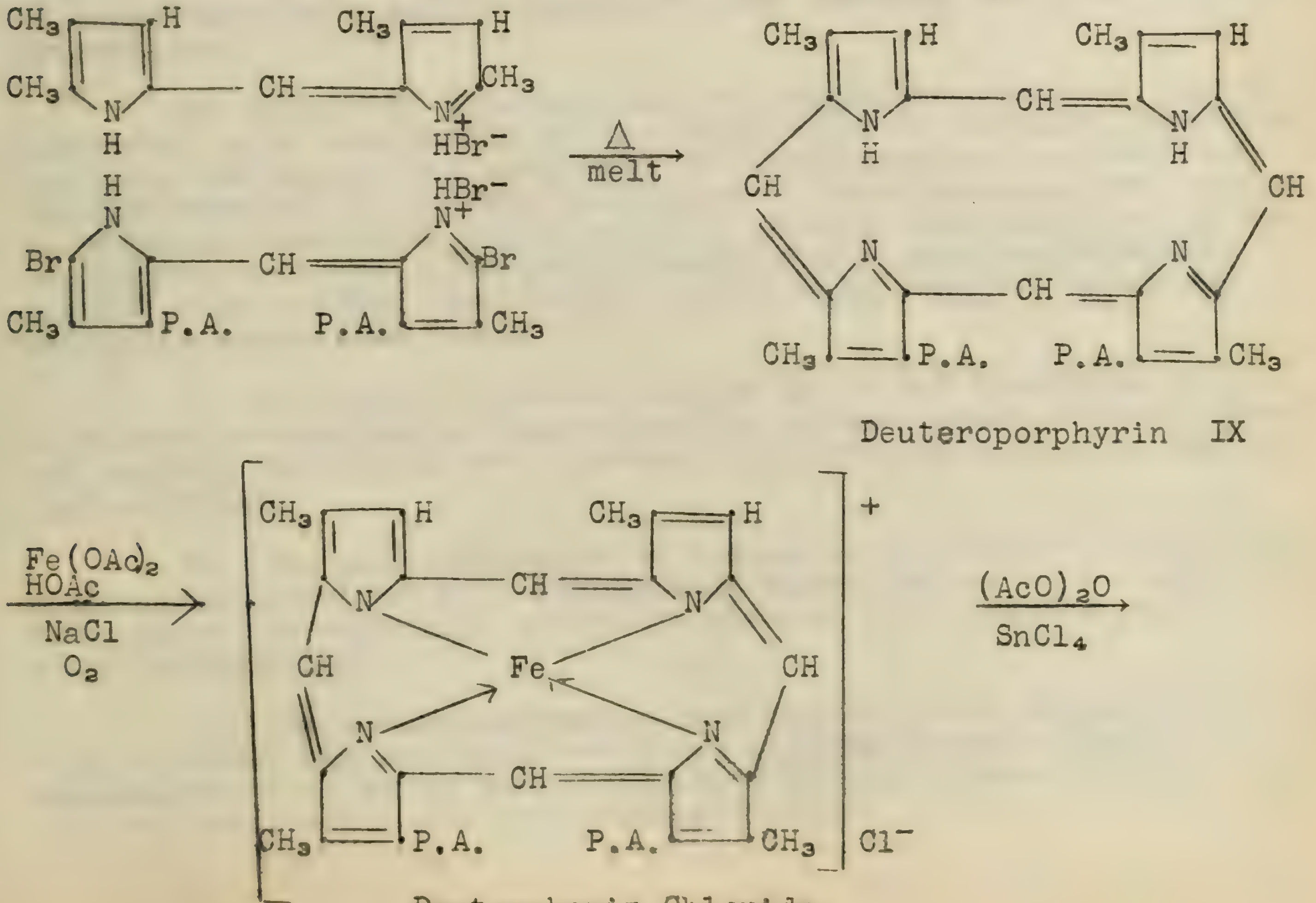
The preparation of ferric-etioporphyrin I chloride (1,3,5,7-tetramethyl-2,4,6,8-tetraethyl porphin) was subjected to some study with the idea in mind of improving the yields. It was found that quantitative yields could be obtained by carrying out the reaction in glacial acetic acid in the presence of the strong base, sodium acetate.

$$\text{Etioporphyrin I} + \text{Fe}^{++} \xrightarrow[\text{HOAc, NaOAc}]{N_2} \text{Ferro-Heme} + 2\text{H}^+$$

$$\text{Ferro-Heme} \xrightarrow[\text{NaCl}]{O_2} \text{Ferri-Lemin Chloride}$$

Definite evidence as to the non-participation of the porphyrin carboxyl groups in the formation of metal complexes is indicated by the fact that alkyl-substituted porphyrins form them readily, and by infrared absorption experiments from this laboratory. The latter investigations showed the complete disappearance of N-H (or N-H-N) absorption when the iron complex of etioporphyrin I was prepared.

The synthesis of blood hemin chloride by Fischer in 1928 earned him the Nobel Prize and is a remarkable contribution to bioorganic chemistry. The synthesis is outlined below:

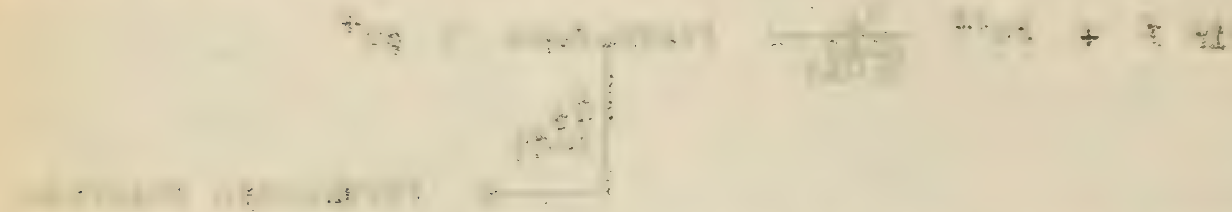


Deuteroporphyrin IX

Deuterohemin Chloride

By modifications of this technique and by several other [illegible], the following metalloporphyrins have been prepared and characterized: Fe, Co, Mn, Ni, Cu, Zn, [illegible], and several others.

The preparation of [illegible] porphyrin I chloride [illegible] [illegible] it was found that satisfactory yields could be obtained [illegible] in glacial acetic acid in the presence of [illegible]



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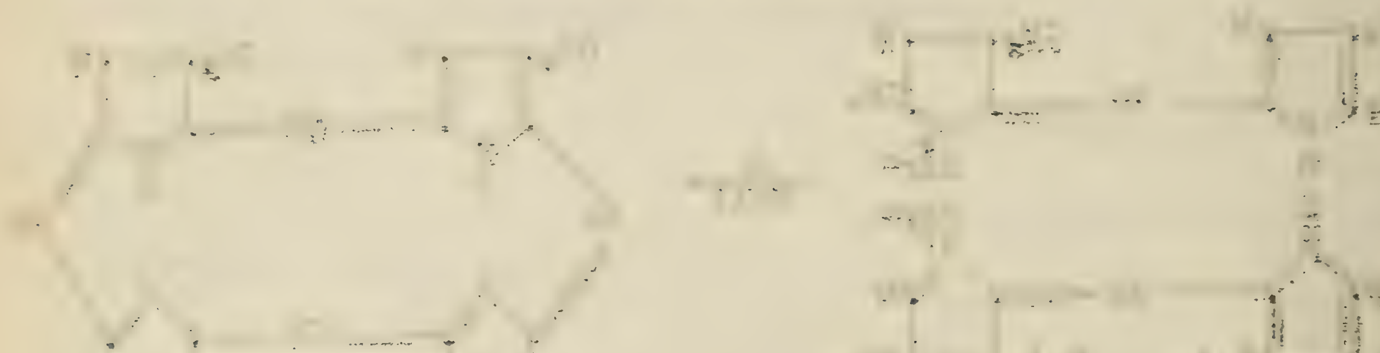
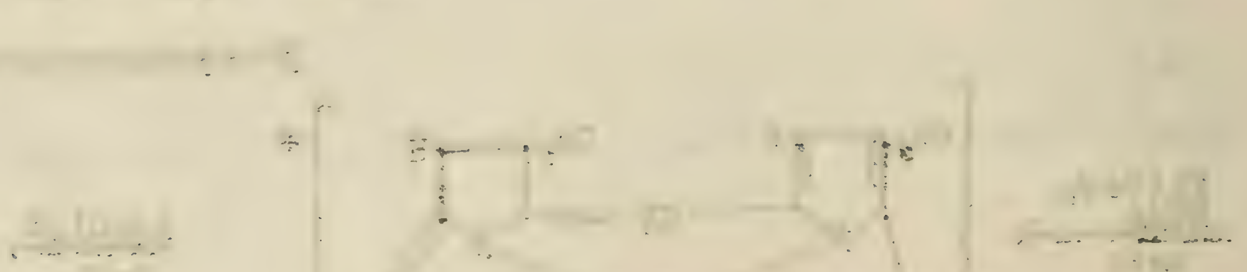
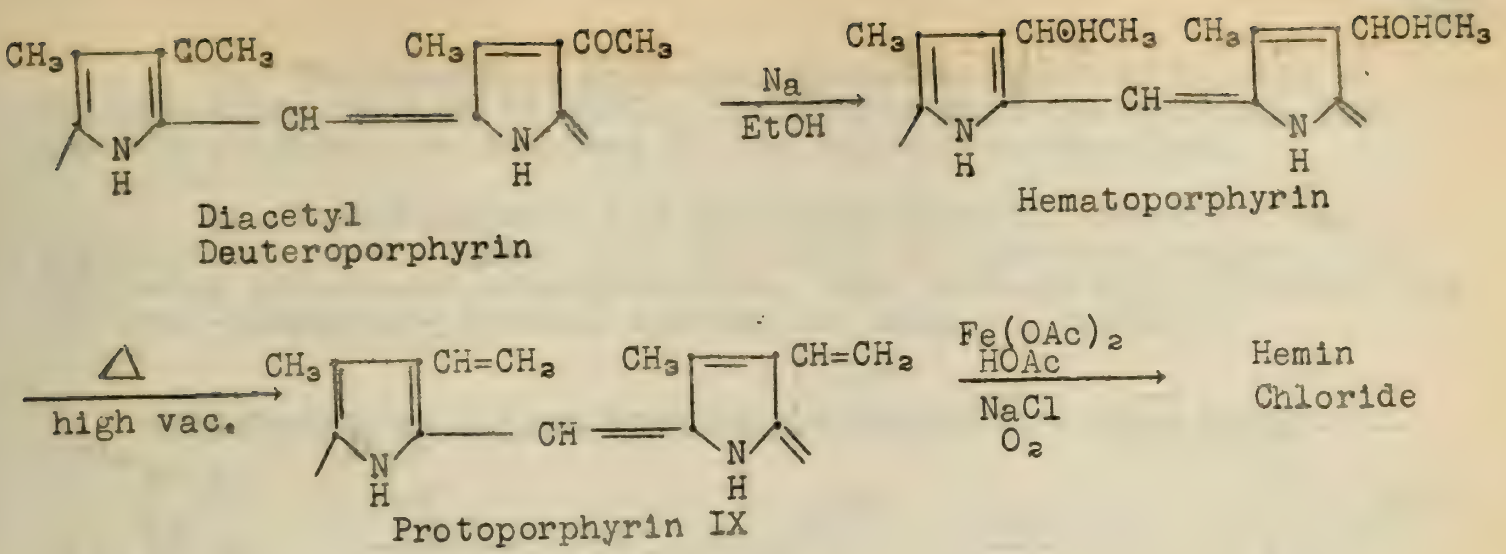
The synthesis of [illegible] is outlined below:







III. Metalloporphyrin Complexes

A favored coordination number for iron is six; hence the iron-porphyrin complexes appear to have two vacancies in their coordination shells, assuming four electron-pair bonds to the porphyrin nitrogens. Metalloporphyrins exhibit a strong tendency to coordinate with donor molecules, such as ammonia, pyridine, cyanide ion, thiocyanate, imidazoles, amines, amino acids, proteins, etc. The donor molecule-metalloporphyrin complexes exhibit marked changes in certain properties as compared to the properties of the metalloporphyrins. Such changes include increased solubility (generally), difference in spectral absorption, a more "positive" oxidation-reduction potential, an electromotively active character, and certain specific catalytic properties.

The effect of modifications of porphyrin structure and of differing metal components on the properties of pyridine, nicotine, cyanide, and α-picoline complexes of metalloporphyrins have been studied recently in Clark's laboratory. These systems were chosen as model systems which would permit a careful investigation of the equilibria involved. The potentiometric and spectrophotometric methods have yielded some rather interesting results, which are partially summarized below:

1. All of the systems studied (with the exception of the iron-protoporphyrin-nicotine system in aqueous solution) are monomers and exhibit reversible one electron oxidation-reduction in the pH region 8-12.5.

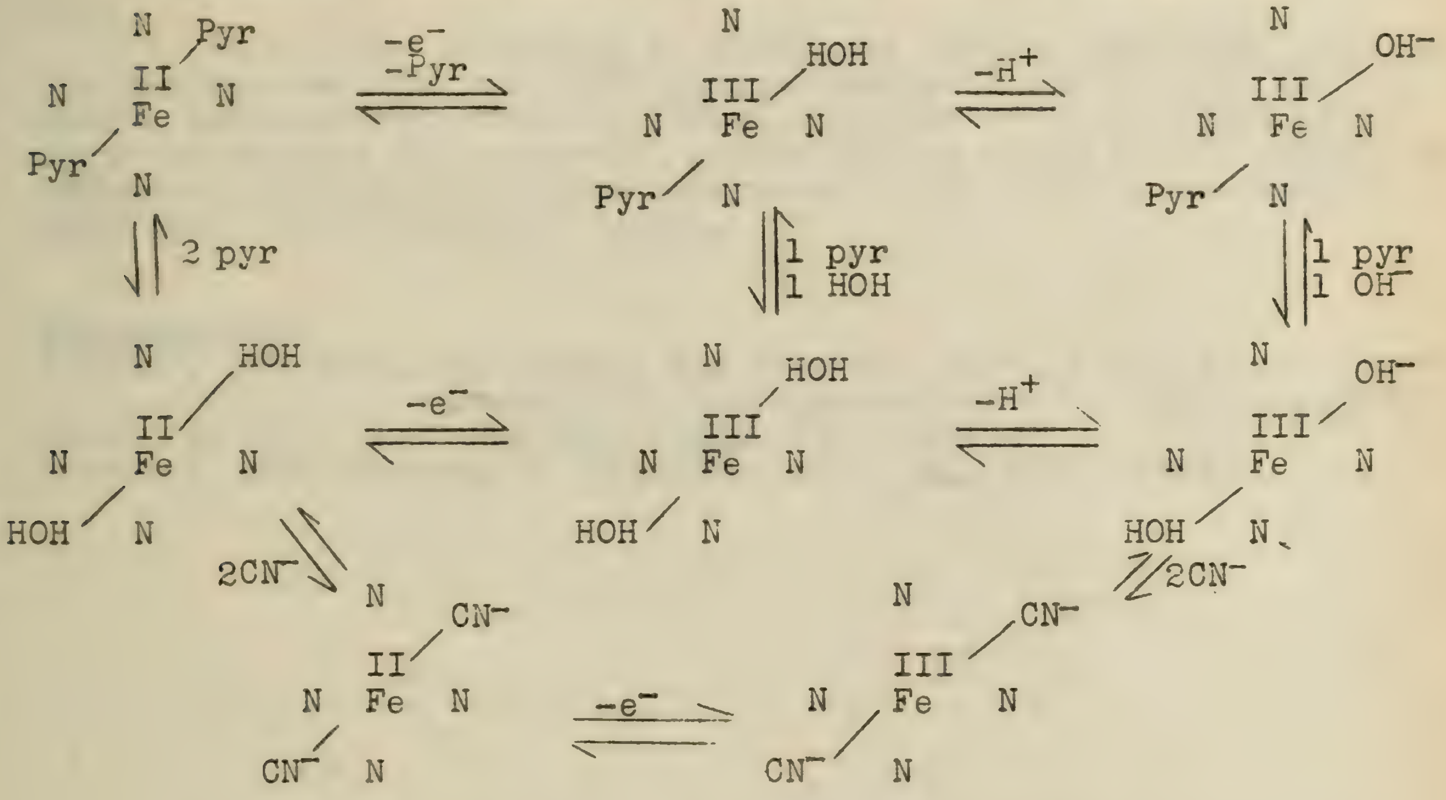
2. The metalloporphyrins become electromotively active and stable when combined with nitrogenous bases and exhibit a more positive oxidation-reduction potential than do the uncoordinated metalloporphyrins.

3. The cobalt-porphyrin-base systems, the manganese-porphyrin base systems, and the iron-porphyrin-cyanide systems show no dependence of E_0' on pH in the region studied. Hence, hydrogen ions are not involved in the oxidation-reduction.

4. The remaining iron-porphyrin-base systems exhibit a dE_0'/dpH slope of 0.06 at 30°C., indicating that one hydrogen ion and one electron are involved in the oxidation-reduction.

5. Potentiometric and spectrophotometric coordination experiments, when coupled with the above information, suggest the following structural interpretation. The iron-porphyrin-cyanide and the iron-porphyrin-pyridine systems are used as examples.

NITROGENOUS BASE-IRON-PORPHYRIN-HYDROGEN ION EQUILIBRIA



We have recently begun a study of the oxygen capacities of substituted heme-globin complexes. Such a study involves porphyrin syntheses and an early stumbling block - namely, the preparation of native globin. We have succeeded in preparing a soluble, pigment-free globin according to the following modification of Anson and Mirsky's original scheme.

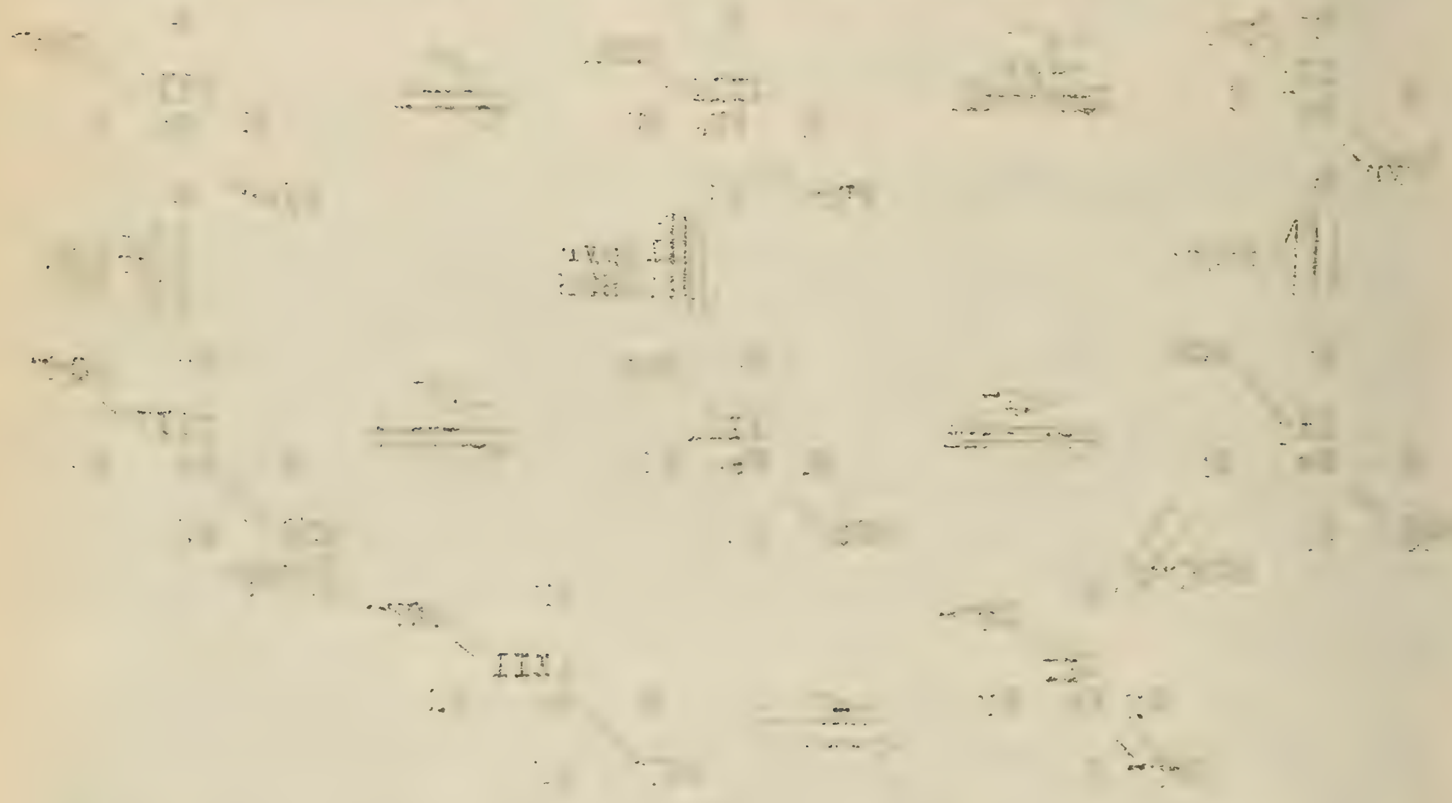
$$HbO_2 \xrightarrow{K_3Fe(CN)_6} Met.Hb \xrightarrow[\substack{0^\circ C \\ 9\ vols.\ Acetone}]{\substack{dil.\ HCl \\ pH\ 3}} Globin.HCl \xrightarrow{\substack{to \\ pH\ 7}} Globin$$

The method above takes advantage of information gained from the model systems, which indicates that ferrous-porphyrins are more tightly bound to coordinating molecules than are ferric-porphyrins. Hence globin is more readily split from methemoglobin (Fe^{+++}) than from oxyhemoglobin (Fe^{++}).

4. The [illegible] Iron-porphyrin-[illegible] [illegible] of 0,06 at 25°C. Indicating that [illegible] involved in the [illegible]

5. [illegible]

[illegible]



[illegible]

[illegible]

[illegible]

[illegible]

Difficulties are also encountered in the quantitative coupling of globin and hemin. According to the following equations we have carried out the coupling reaction under physiological conditions and effected the reduction of the resulting methemoglobin by ascorbic acid at neutral pH.

$$\text{Globin} \xrightarrow[\substack{\text{Buffer} \\ \text{Saline}}]{\substack{\text{Hemin} \\ \text{Chloride}}} \text{Methemoglobin} \xrightarrow[\text{pH 7}]{\substack{\text{Ascorbic} \\ \text{acid}}} \text{Hb} \xrightarrow{O_2} \text{HbO}_2$$

We are now preparing to study the oxygen combining power of the globin complexes of iron-coproporphyrins I and II, and of iron-proto- and mesoporphyrins IX. Such a series of experiments will serve to examine the essential nature of the vinyl groups and of the porphyrin configuration with reference to the ability to combine reversibly with molecular oxygen.

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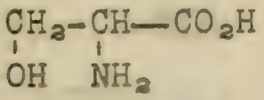
Clark, et al., J. Biol. Chem., 135, 543 (1940).
Vestling and Downing, J. Am. Chem. Soc., 61, 3511 (1939).

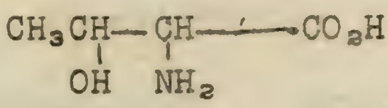
Reported by C. S. Vestling
May 7, 1941

Four hydroxyamino acids - tyrosine, serine, hydroxyproline and threonine - are known to occur in proteins. Two others - hydroxyglutamic acid and hydroxylysine - have been suggested as protein constituents. Of these substances, serine, threonine, and hydroxyglutamic acid are α-amino-β-hydroxy acids.



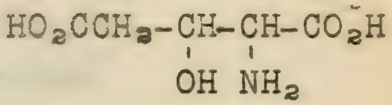
$\underset{OH}{CH_2}-\underset{NH_2}{CH}-CO_2H$

Serine



$CH_3\underset{OH}{CH}-\underset{NH_2}{CH}-CO_2H$

Threonine



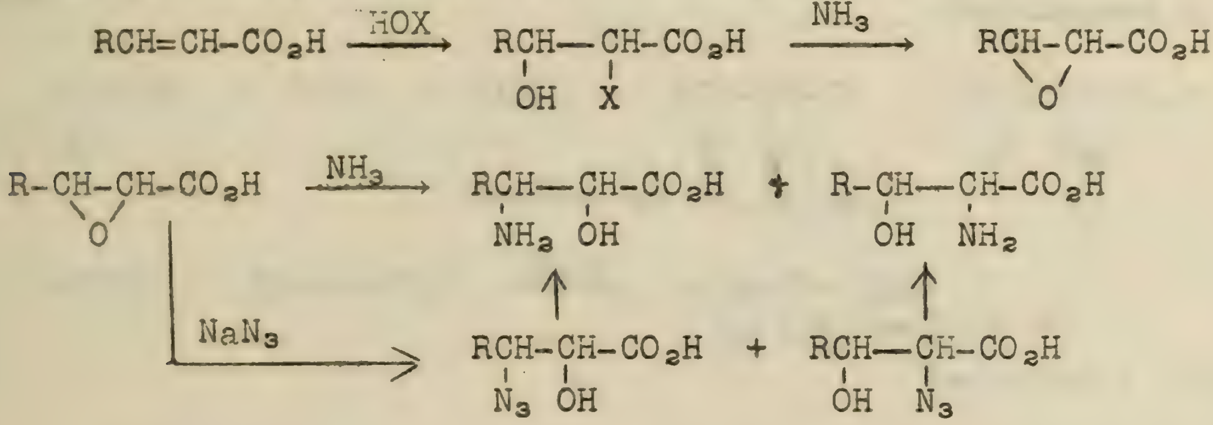
$HO_2CCH_2-\underset{OH}{CH}-\underset{NH_2}{CH}-CO_2H$

Hydroxyglutamic Acid

The following equations illustrate methods of synthesis and reactions of this type of compound.

Methods of Synthesis of Hydroxyamino Acids (References 1-10)

I.

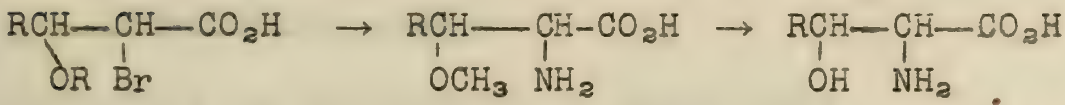


$$RCH{=}CH{-}CO_2H \xrightarrow{HOX} \underset{OH}{RCH}-\underset{X}{CH}-CO_2H \xrightarrow{NH_3} \underbrace{RCH-CH}_{O}-CO_2H$$

$$\underbrace{R-CH-CH}_{O}-CO_2H \xrightarrow{NH_3} \underset{NH_2}{RCH}-\underset{OH}{CH}-CO_2H + \underset{OH}{R-CH}-\underset{NH_2}{CH}-CO_2H$$

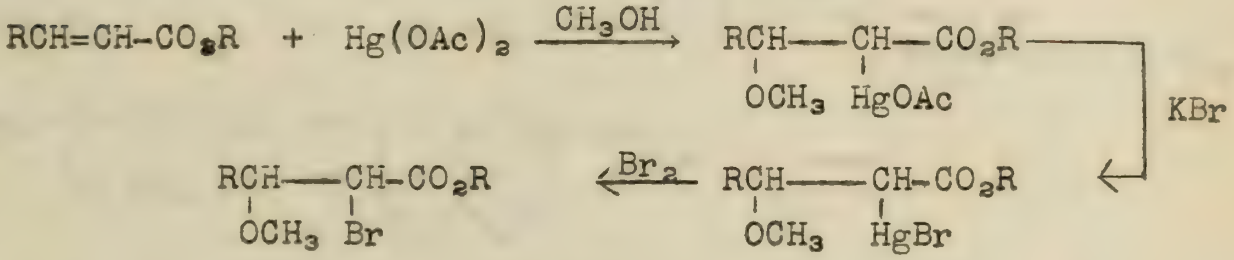
$$\underbrace{R-CH-CH}_{O}-CO_2H \xrightarrow{NaN_3} \underset{N_3}{RCH}-\underset{OH}{CH}-CO_2H + \underset{OH}{RCH}-\underset{N_3}{CH}-CO_2H$$

II.



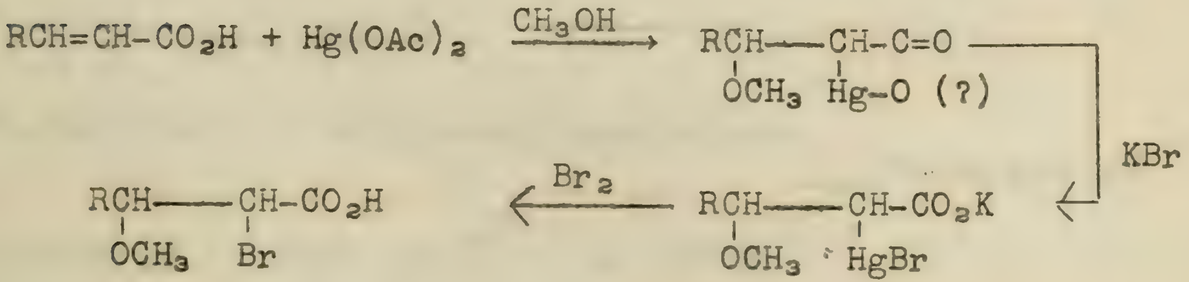
$$\underset{OR}{RCH}-\underset{Br}{CH}-CO_2H \rightarrow \underset{OCH_3}{RCH}-\underset{NH_2}{CH}-CO_2H \rightarrow \underset{OH}{RCH}-\underset{NH_2}{CH}-CO_2H$$

(a)



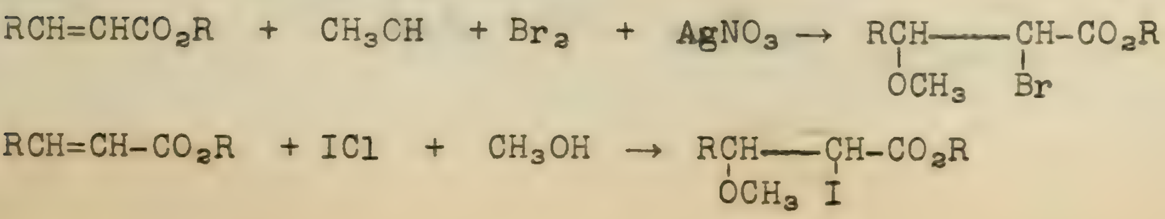
$$RCH{=}CH{-}CO_2R + Hg(OAc)_2 \xrightarrow{CH_3OH} \underset{OCH_3}{RCH}-\underset{HgOAc}{CH}-CO_2R \xrightarrow{KBr} \underset{OCH_3}{RCH}-\underset{HgBr}{CH}-CO_2R \xrightarrow{Br_2} \underset{OCH_3}{RCH}-\underset{Br}{CH}-CO_2R$$

(b)



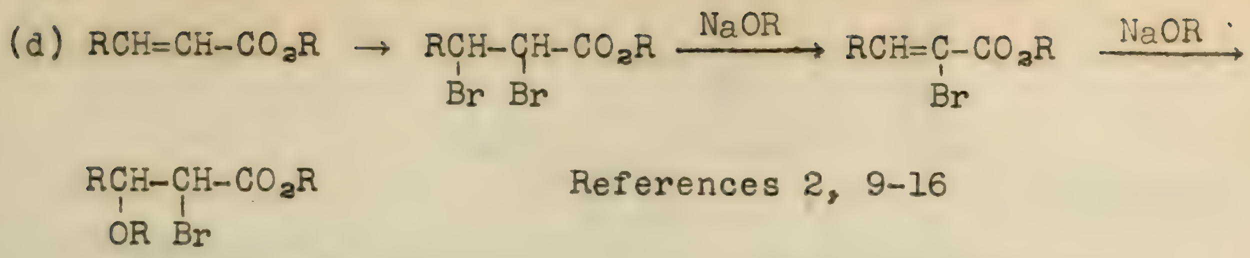
$$RCH{=}CH{-}CO_2H + Hg(OAc)_2 \xrightarrow{CH_3OH} \underset{OCH_3}{RCH}-\underset{Hg-O\ (?)}{CH}-C{=}O \xrightarrow{KBr} \underset{OCH_3}{RCH}-\underset{HgBr}{CH}-CO_2K \xrightarrow{Br_2} \underset{OCH_3}{RCH}-\underset{Br}{CH}-CO_2H$$

(c)



$$RCH{=}CHCO_2R + CH_3CH + Br_2 + AgNO_3 \rightarrow \underset{OCH_3}{RCH}-\underset{Br}{CH}-CO_2R$$

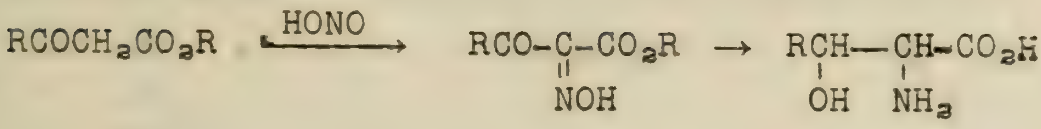
$$RCH{=}CH{-}CO_2R + ICl + CH_3OH \rightarrow \underset{OCH_3}{RCH}-\underset{I}{CH}-CO_2R$$



(d) $RCH{=}CH{-}CO_2R \rightarrow \underset{Br}{RCH}{-}\underset{Br}{CH}{-}CO_2R \xrightarrow{NaOR} RCH{=}\underset{Br}{C}{-}CO_2R \xrightarrow{NaOR}$

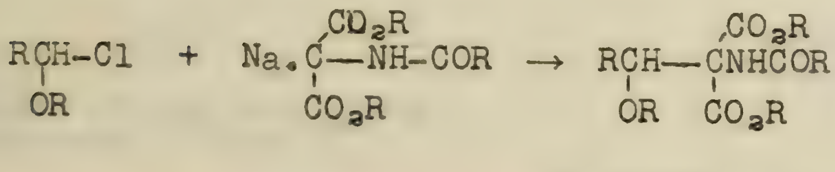
$\underset{OR}{RCH}{-}\underset{Br}{CH}{-}CO_2R$

References 2, 9-16

III. 

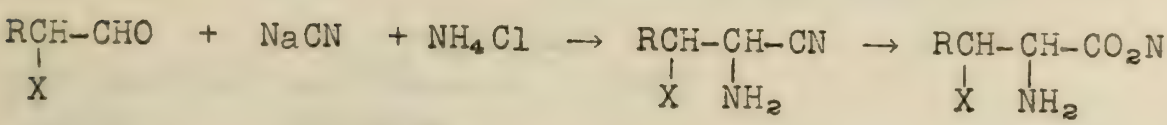
$RCOCH_2CO_2R \xrightarrow{HONO} RCO{-}\underset{NOH}{\overset{}{C}}{-}CO_2R \rightarrow \underset{OH}{RCH}{-}\underset{NH_2}{CH}{-}CO_2H$

References 5,17,18

IV. 

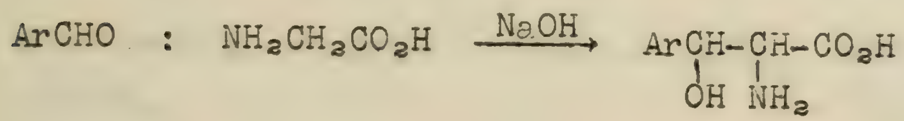
$\underset{OR}{RCH}{-}Cl + Na.\overset{CO_2R}{\underset{CO_2R}{C}}{-}NH{-}COR \rightarrow \underset{OR}{RCH}{-}\overset{CO_2R}{\underset{CO_2R}{C}}NHCOR$

References 2, 19

V. 

$\underset{X}{RCH}{-}CHO + NaCN + NH_4Cl \rightarrow \underset{X}{RCH}{-}\underset{NH_2}{CH}{-}CN \rightarrow \underset{X}{RCH}{-}\underset{NH_2}{CH}{-}CO_2N$

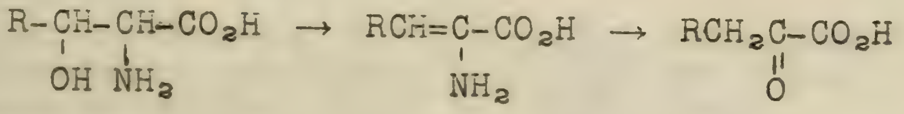
References 20,21,22.

VI. 

$ArCHO : NH_2CH_2CO_2H \xrightarrow{NaOH} Ar\underset{OH}{CH}{-}\underset{NH_2}{CH}{-}CO_2H$

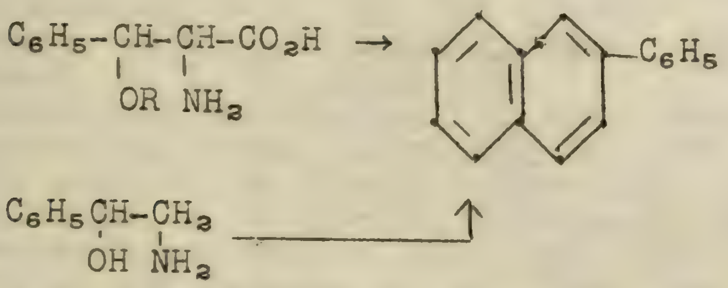
References 23,24,25

Reactions of Hydroxyamino Acids

I. 

$R{-}\underset{OH}{CH}{-}\underset{NH_2}{CH}{-}CO_2H \rightarrow RCH{=}\underset{NH_2}{C}{-}CO_2H \rightarrow RCH_2\underset{O}{\overset{}{C}}{-}CO_2H$

References 5,26,27

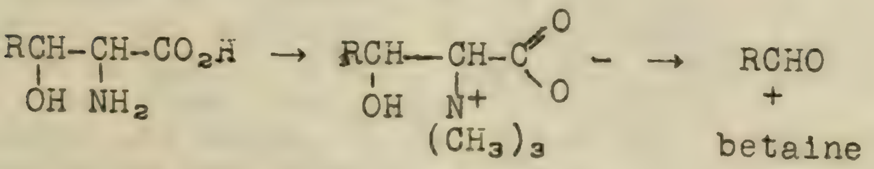
II. 

$C_6H_5{-}\underset{OR}{CH}{-}\underset{NH_2}{CH}{-}CO_2H \rightarrow$

$C_6H_5\underset{OH}{CH}{-}\underset{NH_2}{CH_2}$

$C_6H_5CH_2COCO_2H \rightarrow$ no β-phenylnaphthalene

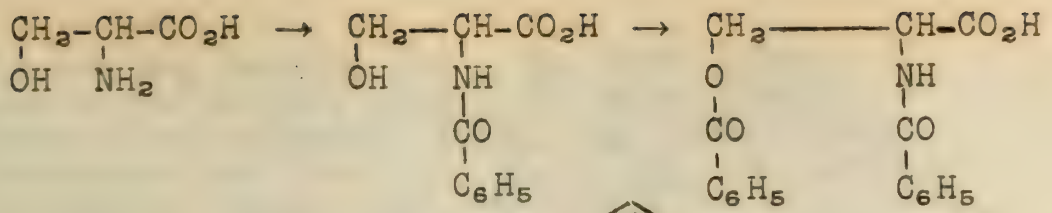
Reference 28

III. 

$\underset{OH}{RCH}{-}\underset{NH_2}{CH}{-}CO_2H \rightarrow \underset{OH}{RCH}{-}\underset{\overset{N+}{(CH_3)_3}}{CH}{-}C\overset{O}{\underset{O}{\lessgtr}}- \rightarrow RCHO + \text{betaine}$

Reference 29

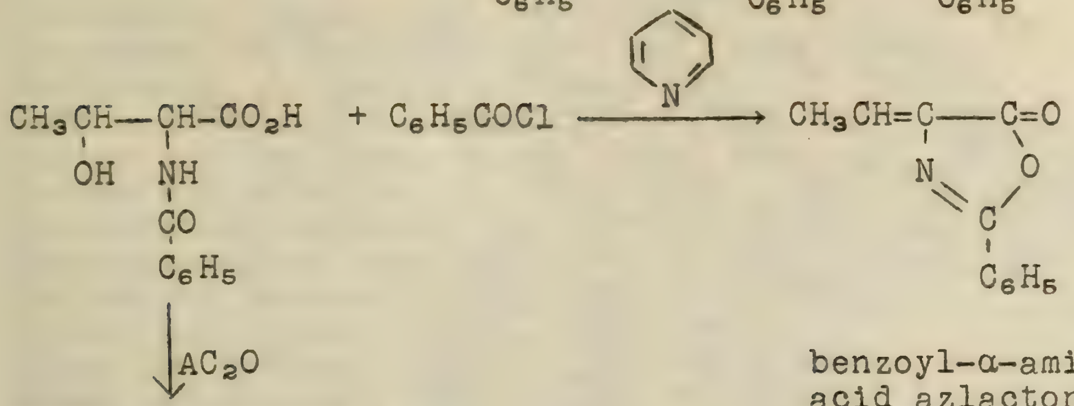
IV.



$\underset{OH}{CH_2}-\underset{NH_2}{CH}-CO_2H \rightarrow \underset{OH}{CH_2}-\underset{\underset{\underset{C_6H_5}{CO}}{NH}}{CH}-CO_2H \rightarrow \underset{\underset{\underset{C_6H_5}{CO}}{O}}{CH_2}-\underset{\underset{\underset{C_6H_5}{CO}}{NH}}{CH}-CO_2H$

Reference 30

V.

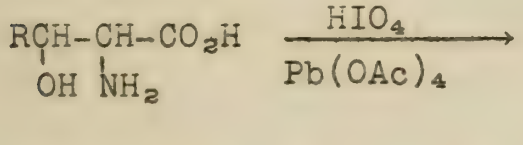


Mixture of cis and trans azlactones (I and II)

benzoyl-α-aminocrotonic acid azlactone I

References 31, 32, 33

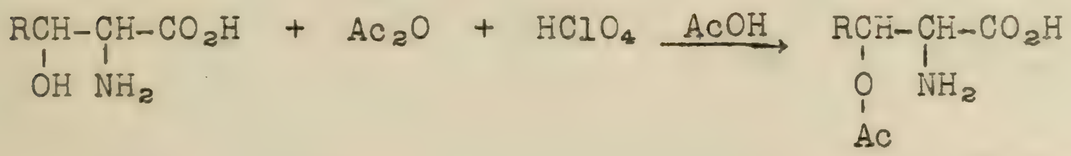
VI.



$R\underset{OH}{CH}-\underset{NH_2}{CH}-CO_2H \xrightarrow[Pb(OAc)_4]{HIO_4} RCHO$

References 34,35,36

VII.



$R\underset{OH}{CH}-\underset{NH_2}{CH}-CO_2H + Ac_2O + HClO_4 \xrightarrow{AcOH} R\underset{\underset{Ac}{O}}{CH}-\underset{NH_2}{CH}-CO_2H$

Reference 37

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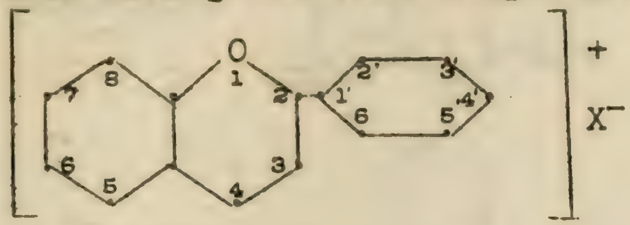
Reported By H. E Carter
May 7, 1941

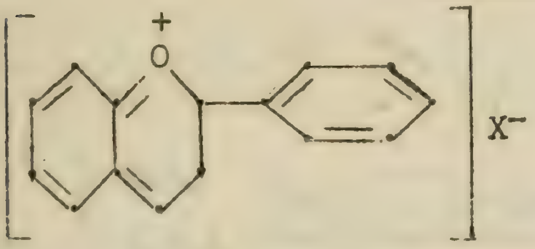
The flavylium salts (2-phenylbenzopyrylium salts) are a class of compounds having the following fundamental nucleus:



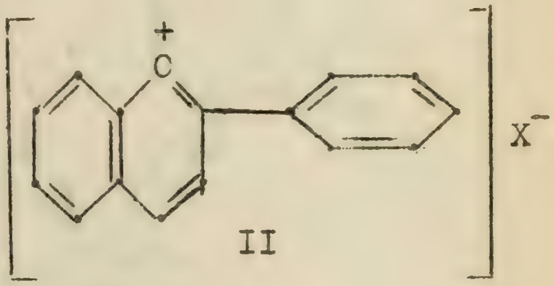
The anthocyanins (red and blue coloring matter in flowers, fruit, etc.) are all polyhydroxy (or methoxy) derivatives of this class.

The carbon and oxygen skeleton structure of the flavylium salts has long been regarded as established, but the point of attachment of the negative ion, the nature of the bond, and the position of the double bonds in the molecule have been the subject of much speculation. Of the many suggested formulas, the following are the most important.

Oxonium Salts

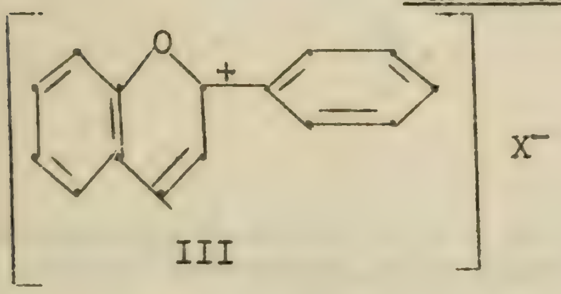


I

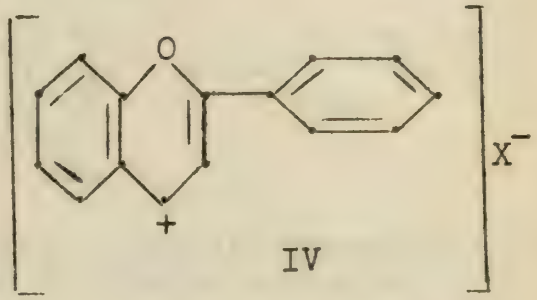


II

Carbonium Salts

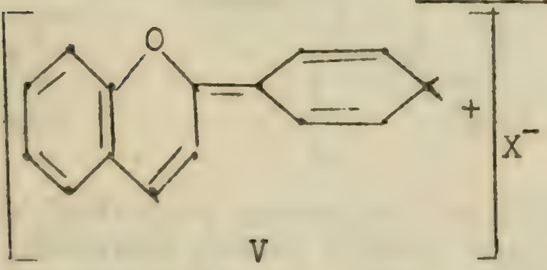


III

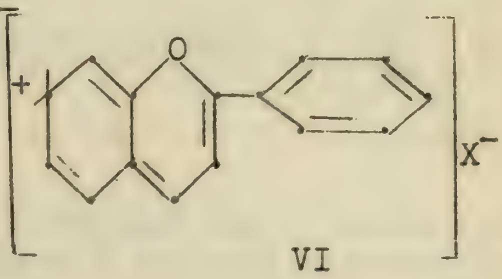


IV

p-Quinoid Forms



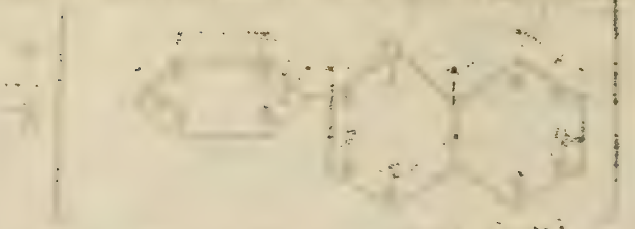
V



VI

All methods of synthesis of benzopyrylium salts have so far yielded only a single salt, even when methods were employed which might be expected to lead to two isomeric structures. This indicates that an allylic shift or resonance must take place. Thus, properly substituted coumarins and chromones yield only a single salt when treated with the proper Grignard reagents.

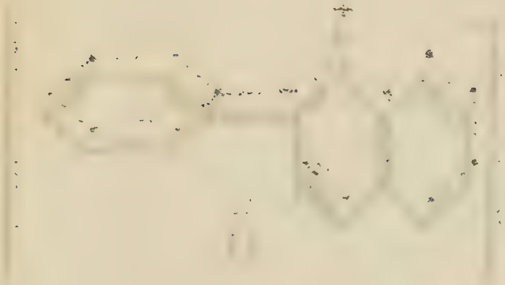
The flavylium salts (2-ph[illegible] [illegible] class of compounds having the following fundamental nucleus:



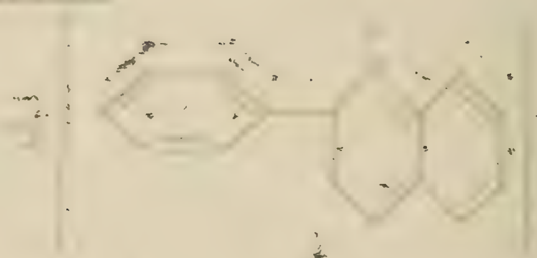
[illegible] anthocyanidins [illegible] which are all [illegible]

[illegible] of the flavylium salts [illegible] and the position of the double bonds in the molecule [illegible] of such structures. Of the many suggested [illegible], the following are the most important.

Oxonium Salts

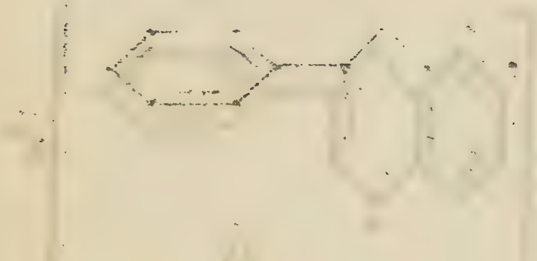


II

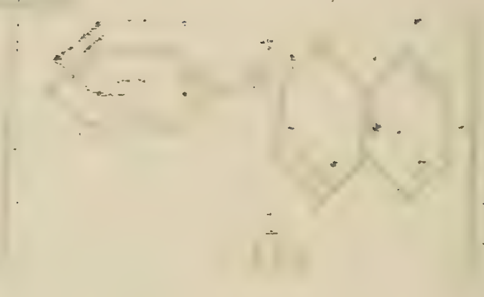


I

Carbonium Salts

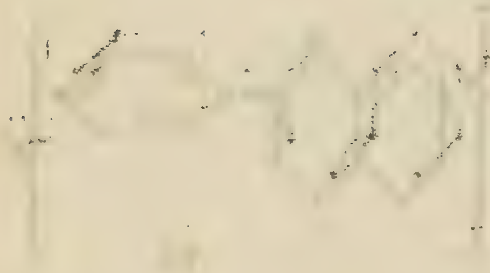


IV

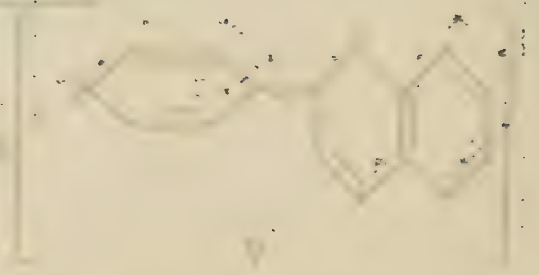


III

Quinoid Forms

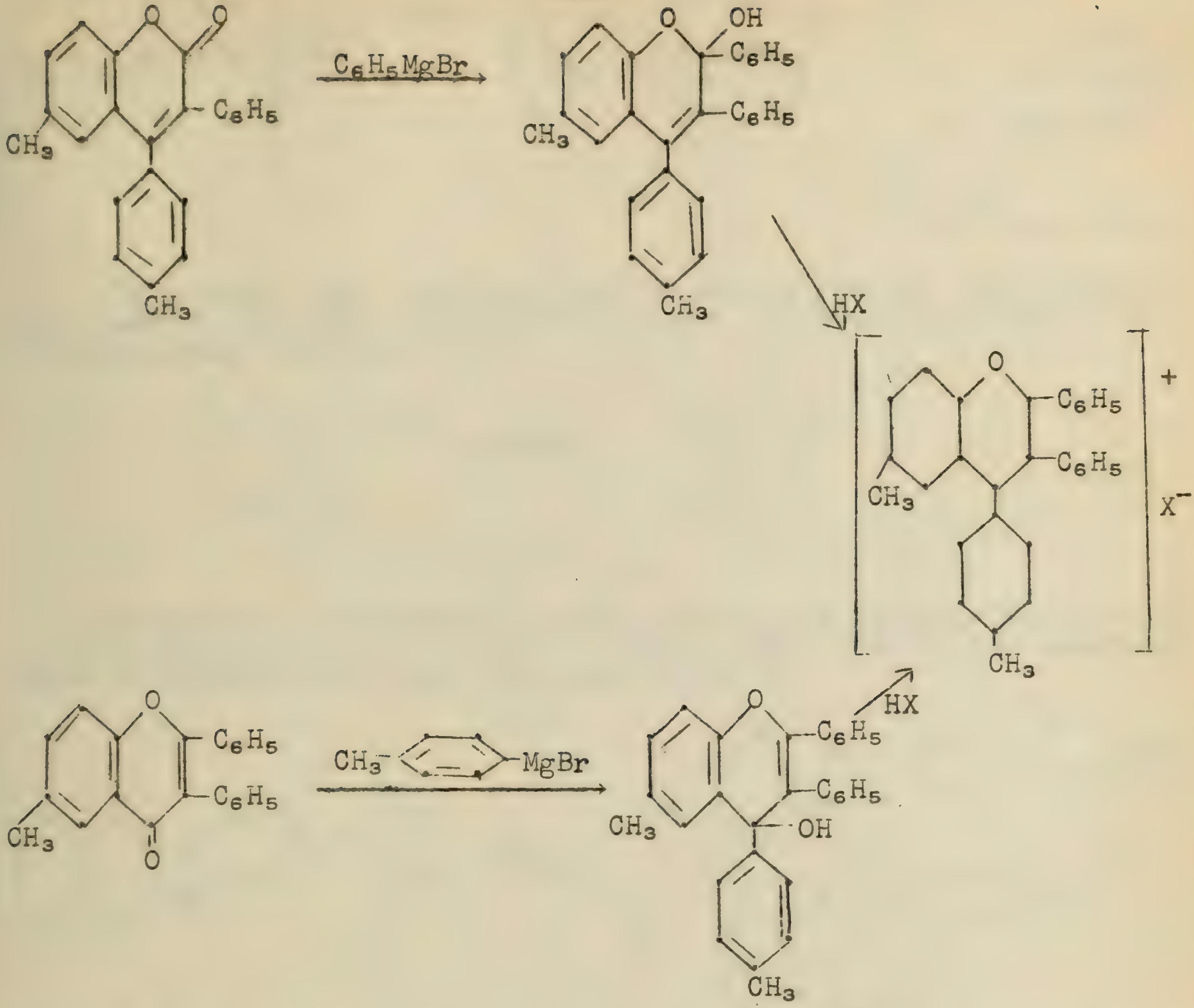


VI

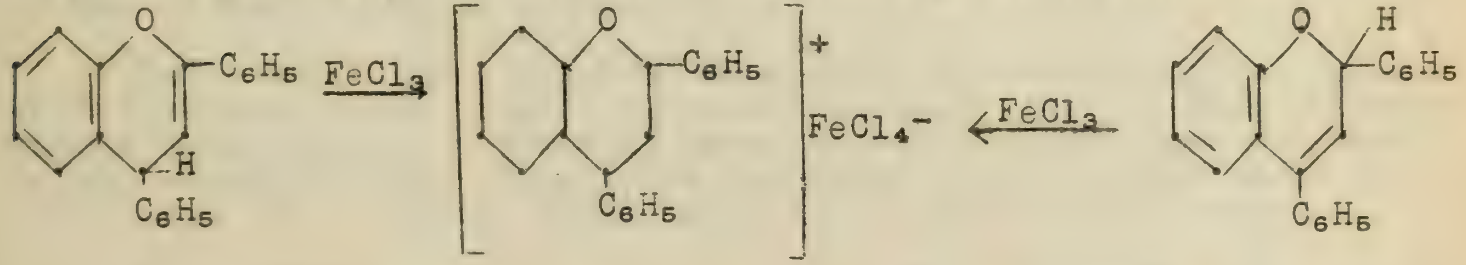


V

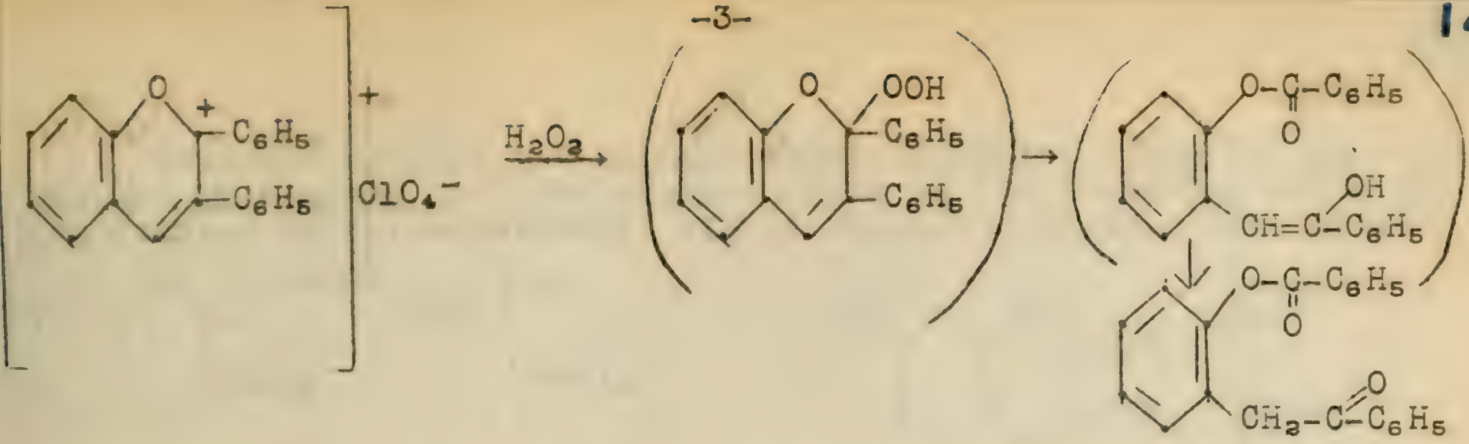
All methods of synthesis of benzopyrylium salts [illegible] yielded only a single salt, [illegible] This indicates that [illegible] Thus, properly substituted [illegible] single salt when treated with the proper [illegible]



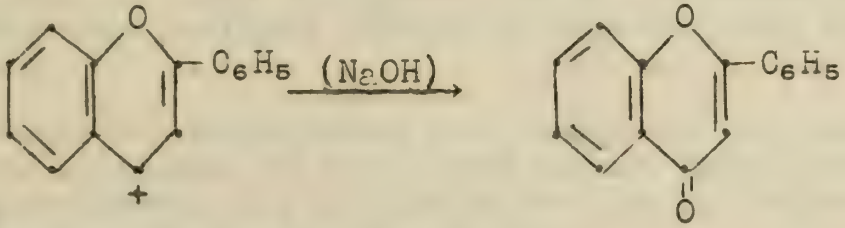
Similarly Lowenbein has shown that two isomeric chromenes yield only a single flavylium salt when oxidized by ferric chloride.



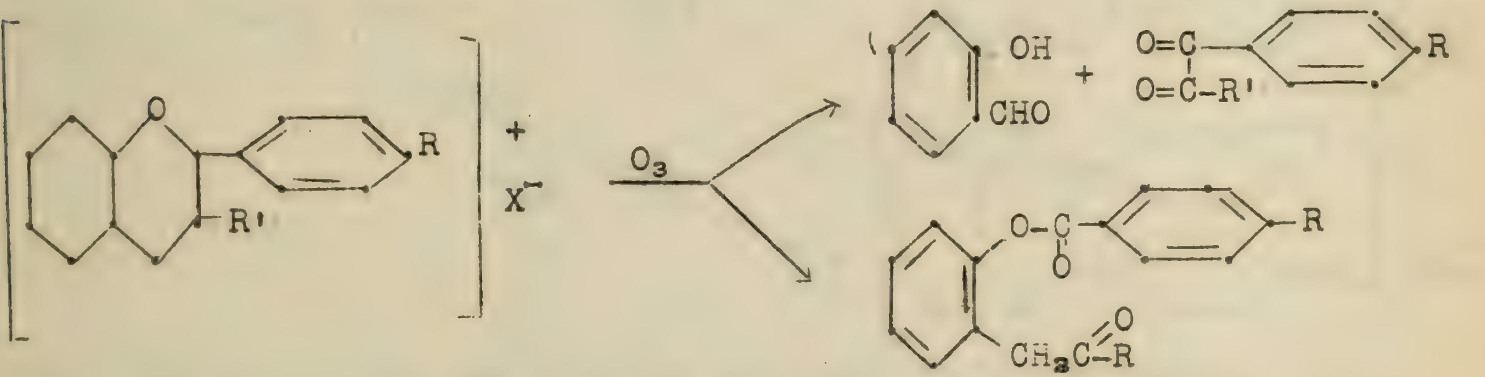
By hydrogen peroxide oxidation of flavylium salts Dilthey obtained products which showed that the ring was cleaved between the 2- and 3-carbon atoms. From this he postulated that the 2-carbon atom is heteropolar (formula III)



In certain cases Hill was able to obtain flavone from flavylium salts and he therefore postulated that the 4-carbon atom may sometimes be heteropolar (formula IV).

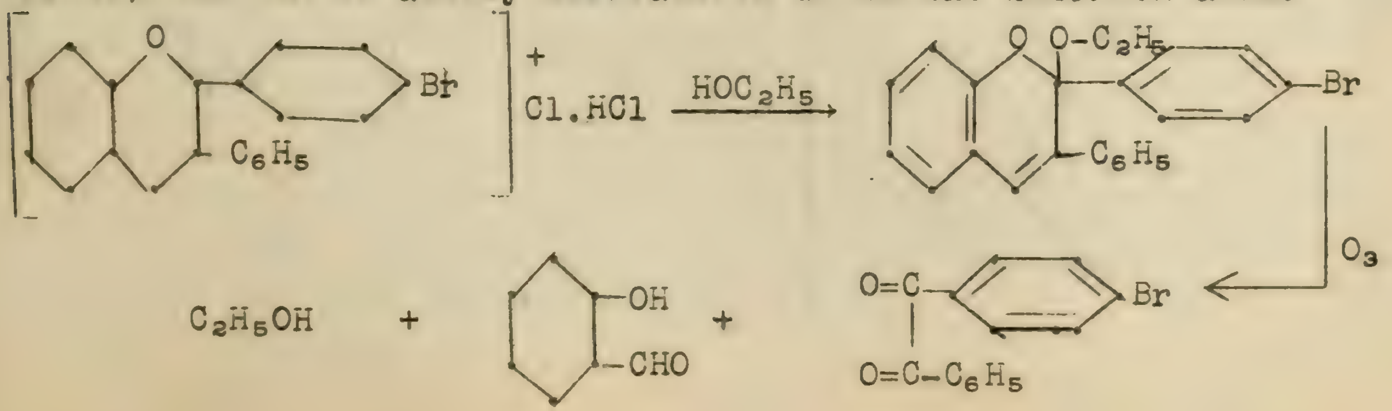


Ozonization of several flavylium salts has given products which indicate that they may be cleaved either between the 2- and 3-carbon atoms or between the 3- and 4-carbon atoms.

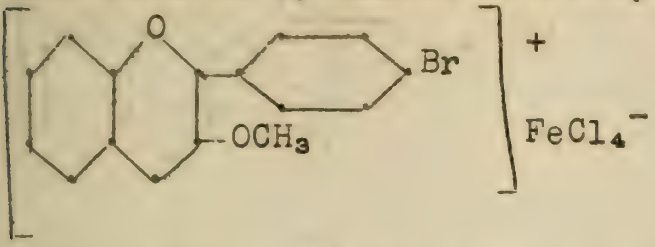


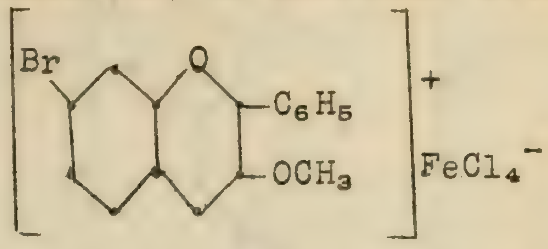
This constitutes the best evidence that the flavylium salts consist of two or more forms in resonance.

Many workers have observed that water or alcohols react easily with flavylium salts to give pyranols or their ethers. Some investigators have placed the entering group on the 2-carbon atom and some on the 4-carbon atom. Ozonolysis has shown that (in some cases at least) the -OR of alkoxy derivatives is on the 2-carbon atom.



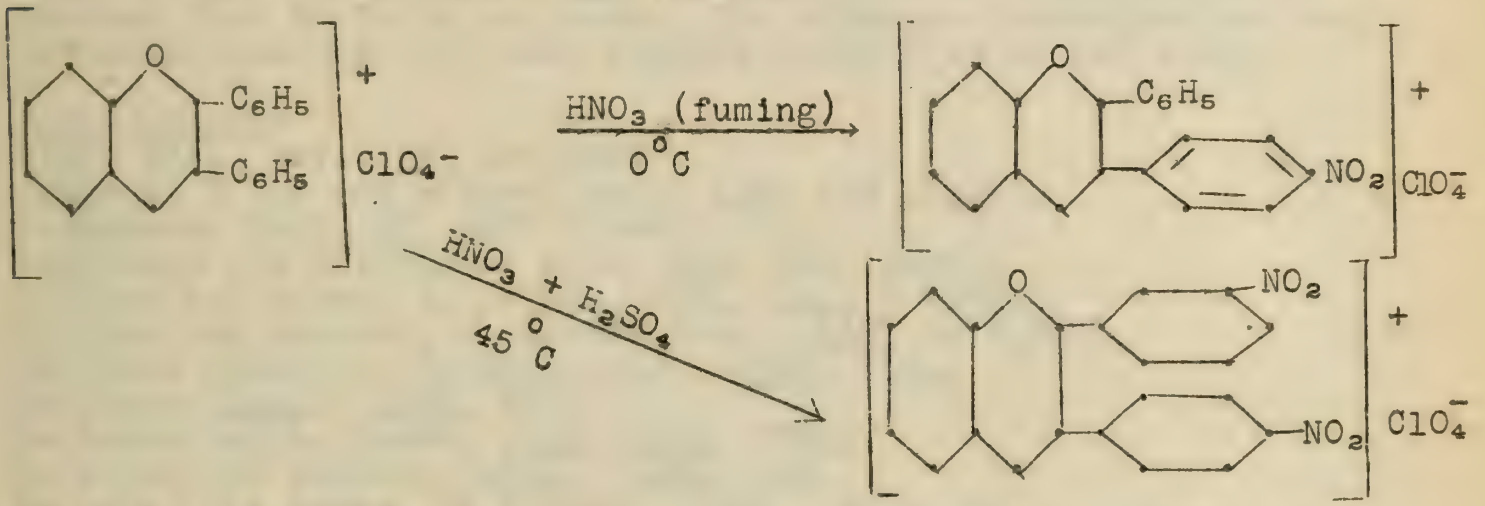
Evidence against thr quinoid forms (formulas V and VI) has been secured by finding that the bromine atoms in the following salts are not removed by silver nitrate, silver chloride, or molecular silver.





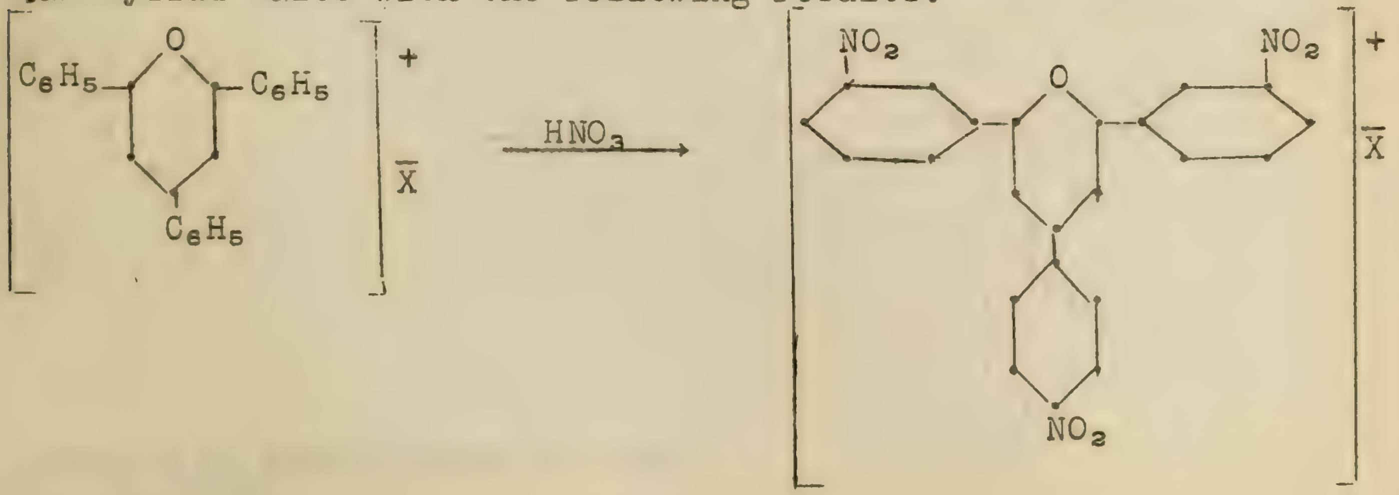
Lowenbein has shown that flavylium salts undergo a simple coupling reaction with Grignard reagents, whereby the R group of RMgX may become attached to either the 2- or 4-carbon atom. This indicates that the positive charge of the salt may be an ether of these atoms.

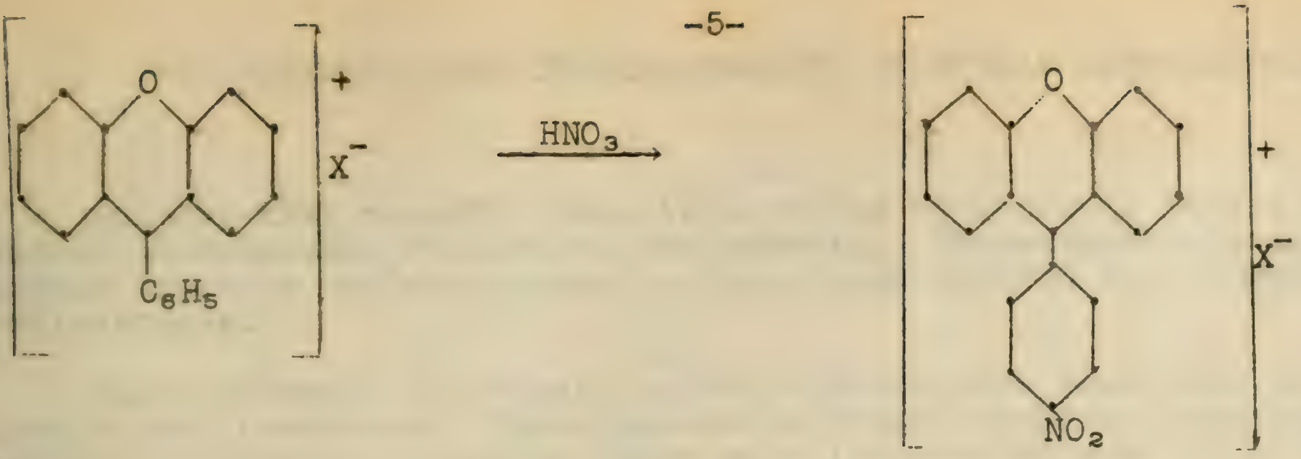
One method of determining the charge on an atom is to observe the directive influence of that atom toward substitution into a benzene ring attached to it. The nitration of 3-phenylflavium perchlorate gives the following results.



This indicates that the 3-carbon atom is relatively negative and that the 2-carbon atom is relatively positive.

LeLevre has also investigated the nitration of pyrylium and xanthylium salts with the following results:





This seems to show that at least in one resonance form of these salts the carbon atom para to the heterocyclic oxygen must be neutral or negative. This might be explained by the existence of the oxonium form, II, in resonance with the two carbonium forms, III and IV.

Conductivity and molecular weight measurements in nitrobenzene show that the perchlorate and ferrichloride of these salts are ionized from 50 to 90 per cent. The chloride hydrochlorides and bromides, however, are only ionized about 3 to 15 per cent.

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Le Levre and Le Levre, ibid, 1932, 2894.
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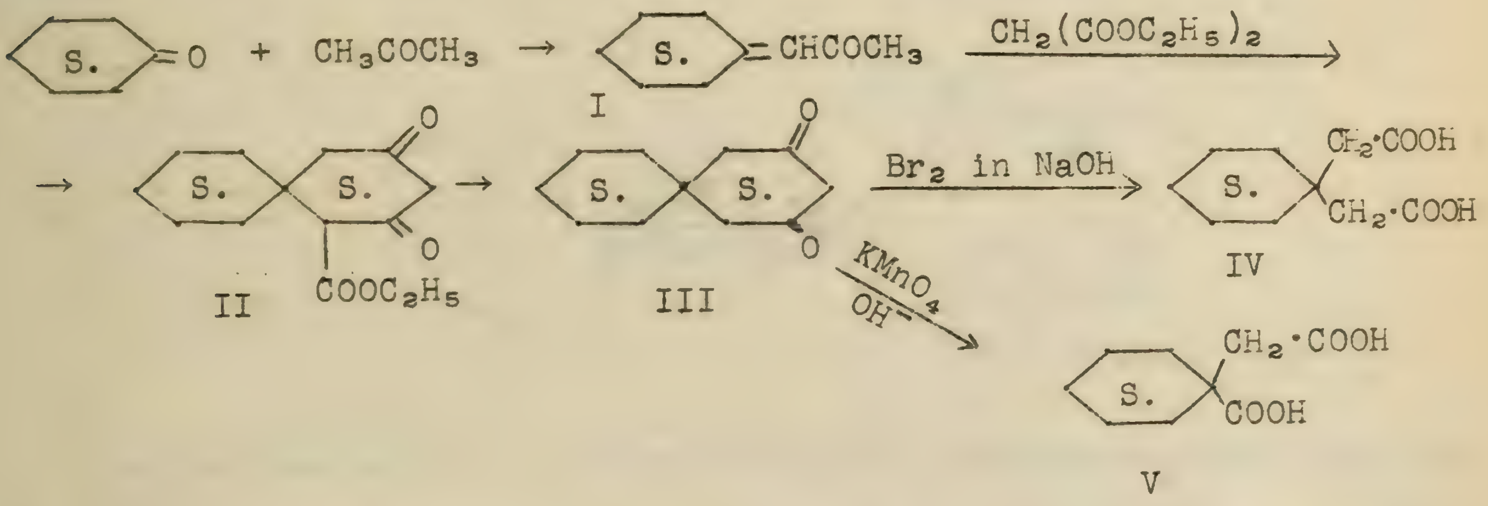
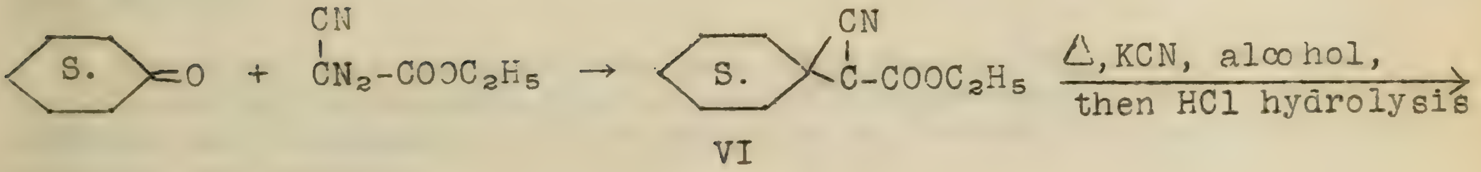
Reported by Robert Bruce Moffett
May 14, 1941

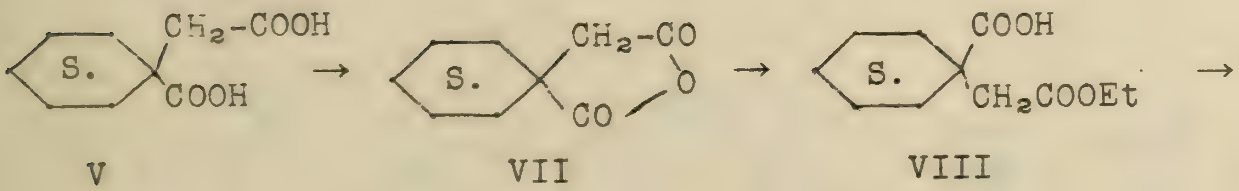
THE SYNTHESIS AND DEHYDROGENATION OF SPIRAN HYDROCARBONS

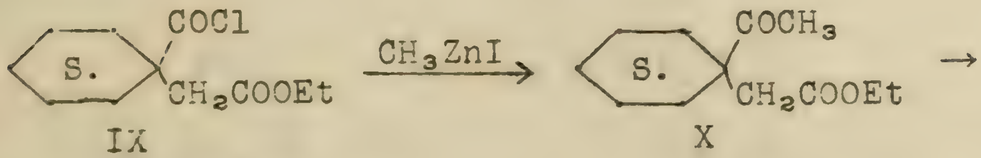
Spirans have recently been isolated as by-products in the cyclization of compounds related to the sterols. Their synthesis and their unique behavior on dehydrogenation have been studied in a number of publications.

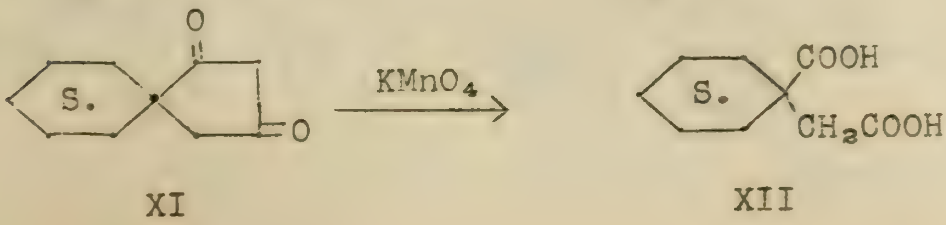
Early attempts to prepare spiran hydrocarbons were made by Thorpe, Ingold, and coworkers. Their papers have been reviewed in a series of articles by Hunter. Some of their more interesting work is outlined below.





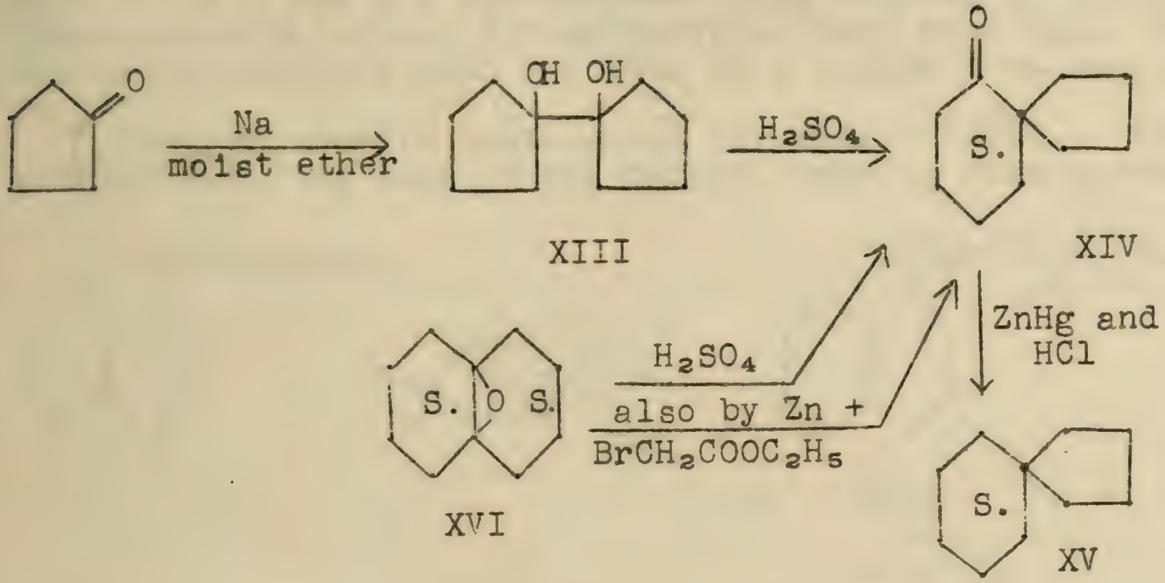






A compound analogous to III was produced when the cyclohexanone was replaced by cyclopentanone. Their closest approach at synthesizing spiran hydrocarbons was the diketones (III and XI).

Clemo and Ormston later prepared cyclohexanespirocyclopentane (XV) by the reduction of 2-ketocyclohexanespirocyclopentane (XIV), which was obtained by three methods:



XIII

XIV

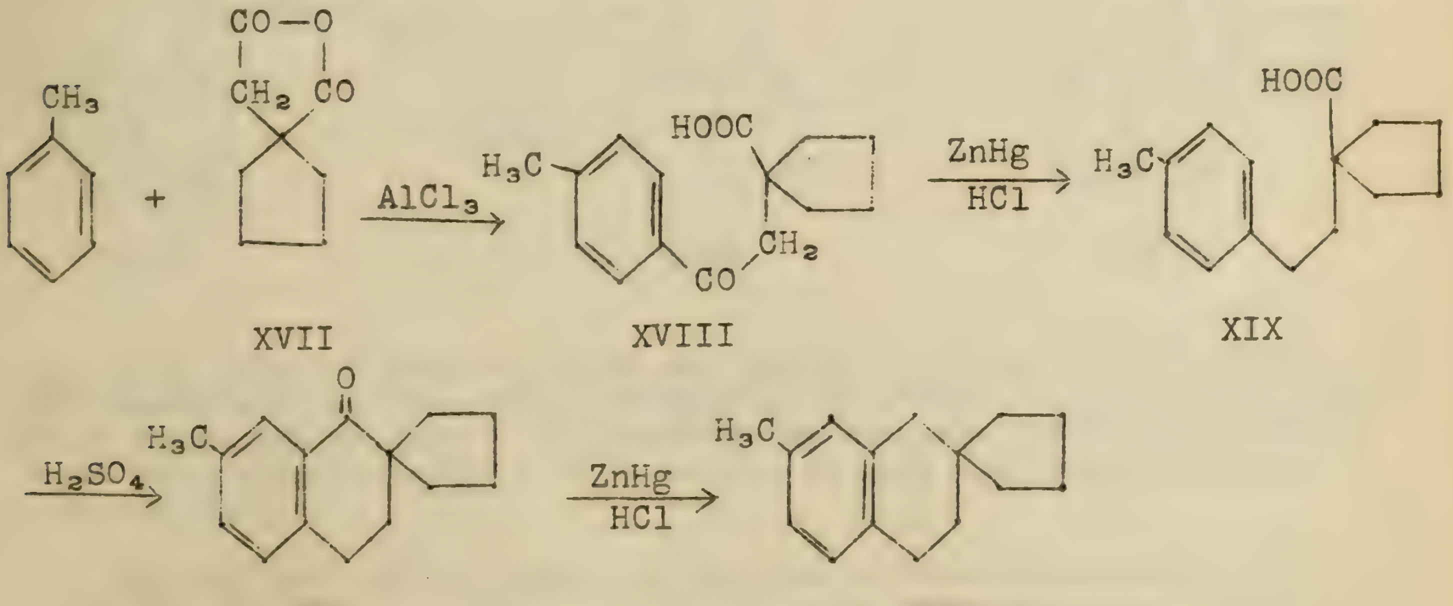
XVI

XV

On dehydrogenation of XV with selenium, naphthalene was obtained.

Zelinsky and Schnikin also prepared XV by a Wolff-Kishner reduction of XIV.

Sen-Gupta has prepared two new spirans, 7-methyl and 7-ethyl-1,2,3,4-tetrahydronaphthalene-2,2-spirocyclopentane (XXI). The former compound was dehydrogenated by selenium to 3-methyl phenanthrene and β-methyl anthracene.



XVII

XVIII

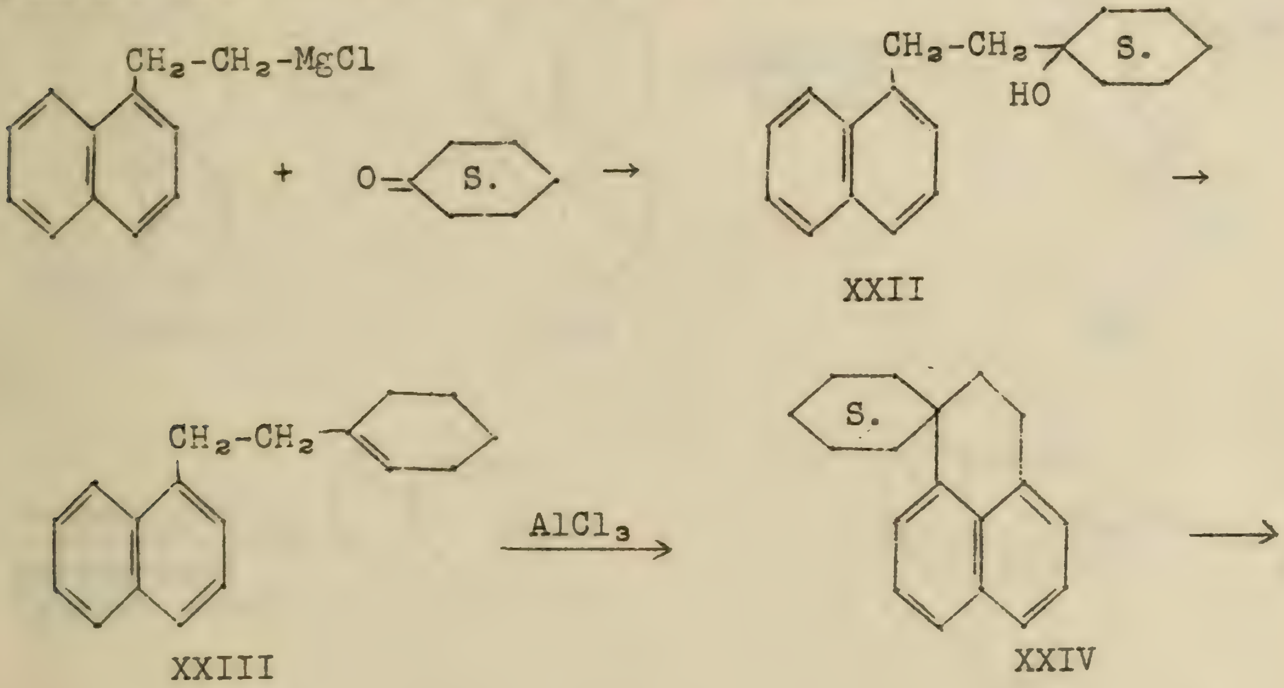
XIX

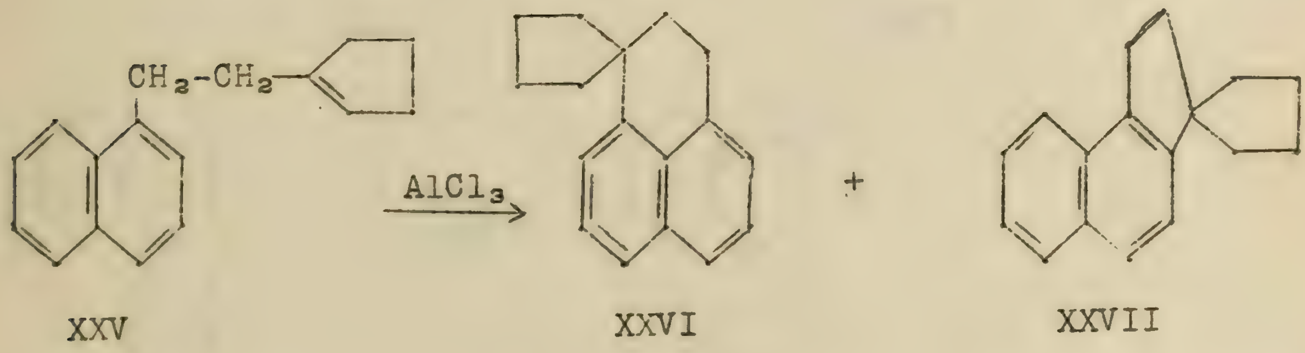
XX

XXI

By replacing the toluene in the above syntheses with (a) naphthalene, (b) α-methyl naphthalene, and (c) hydrindene, he carried out analogous syntheses to produce (a) tetrahydrophenanthrene-2,2-spirocyclopentane, (b) 9-methyl tetrahydrophenanthrene-2,2-spirocyclopentane, and (c) 6,7-cyclopenteno-1,2,3,4-tetrahydronaphthalene-2,2-spirocyclopentane. On dehydrogenation, (a) gave chrysene, (b) gave 3-methyl-1,2-benzanthracene, and (c) gave a compound postulated to be 2,3-cyclopentenoanthracene. When the same synthesis was carried out with benzene and the six-membered ring homolog of XVII, 1,2,3,4-tetrahydronaphthalene-3,3-spirocyclohexane resulted. This compound was dehydrogenated with the loss of a carbon atom to give phenanthrene.

Cook and Hewett synthesized the spiran (XXIV). This was dehydrogenated with the loss of two carbon atoms to form pyrene.



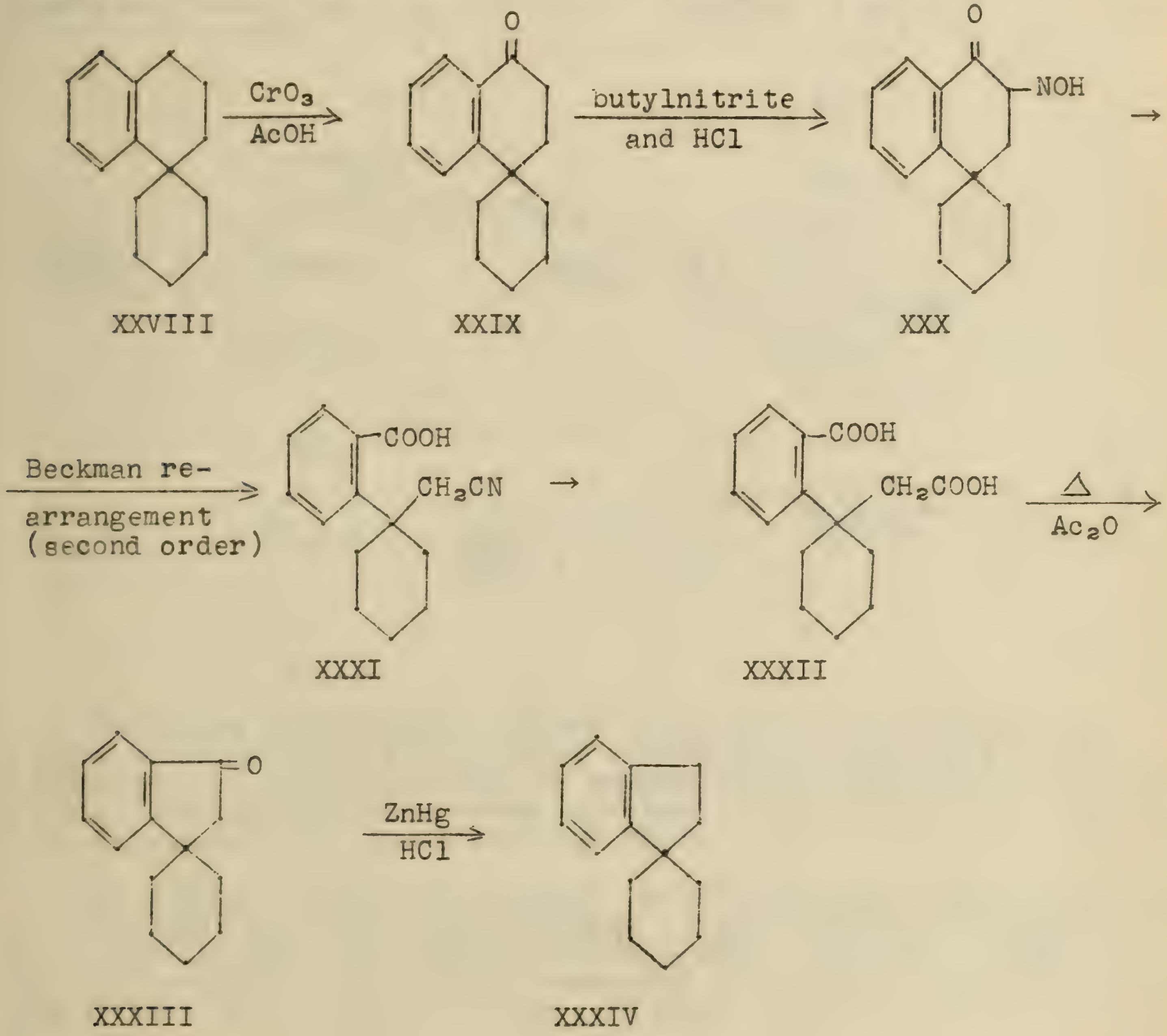


In a similar manner, Cook and Barry replaced cyclohexanone by cyclopentanone in the above synthesis to produce the olefin (XXV), which cyclized to give a mixture of the spirans (XXVI and XXVII). These were dehydrogenated to 2-methyl pyrene and chrysofluorene respectively.

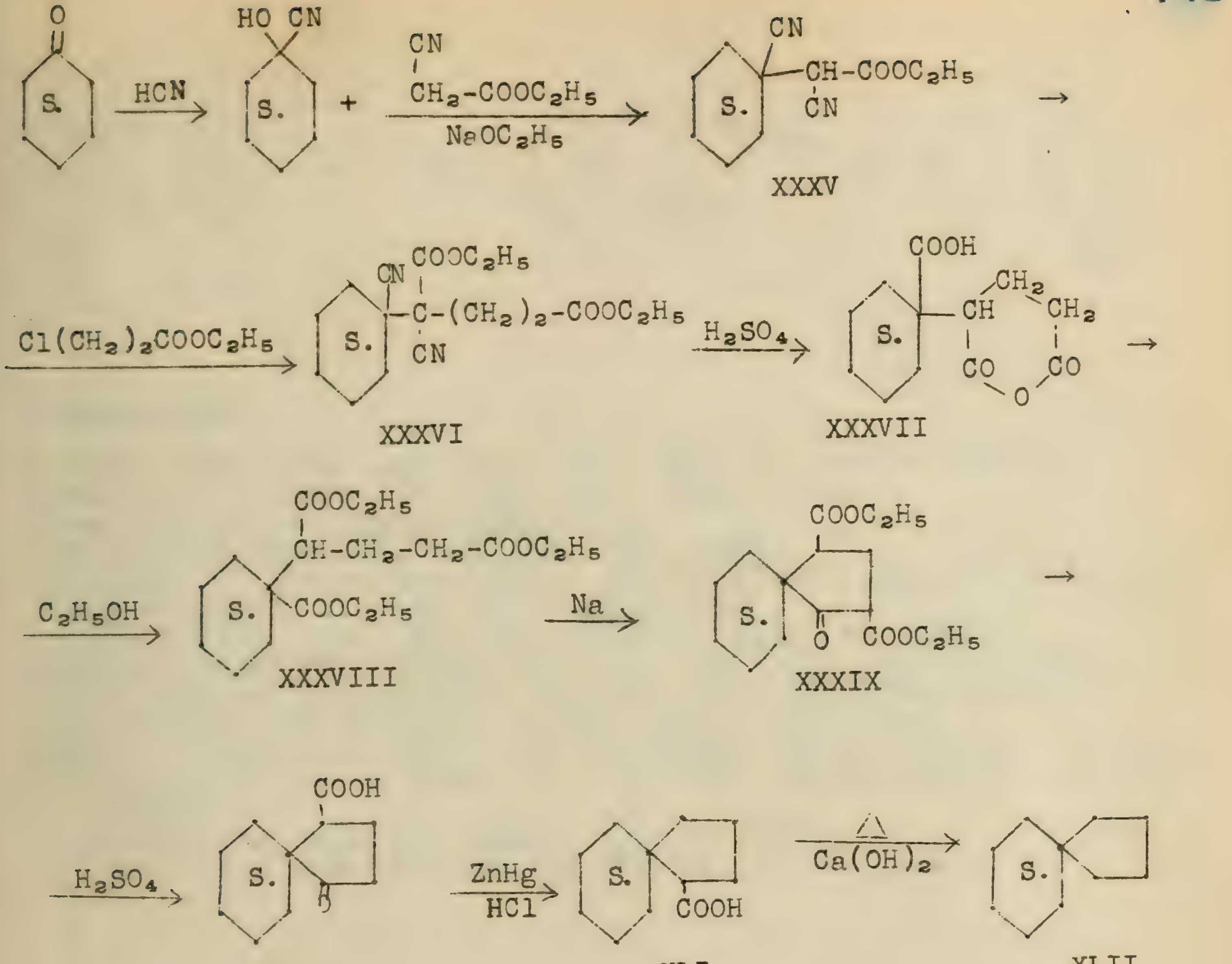
Bogert and others prepared spirans by the cyclodehydration of compounds related to XXII. Thus with the cyclohexanone derivative having three carbons in the chain between the rings (homolog of XXII) and with the corresponding cyclopentanone derivative, he synthesized

spirocyclohexane-1,1-tetralin (XXVIII) and spirocyclopentane-1,1-tetralin. Attempts to dehydrogenate these compounds with selenium failed.

By the cyclodehydration of 1-beta-phenylethylcyclohexanol-1, Bogert and others obtained a mixture of cis- and trans-octahydrophenanthrene and a new spiran. Dehydrogenation of the spiran over palladium and charcoal produced considerable phenanthrene, while at higher temperatures anthracene was obtained. This spiran was shown by synthesis to be spirocyclohexane-1,1-indane (XXXIV).



Chatterjee has reported a general synthesis for spirans. But for a very low yield on the last step (decarboxylation of XLI), the reactions were fairly satisfactory. XLI was dehydrogenated to give naphthalene.

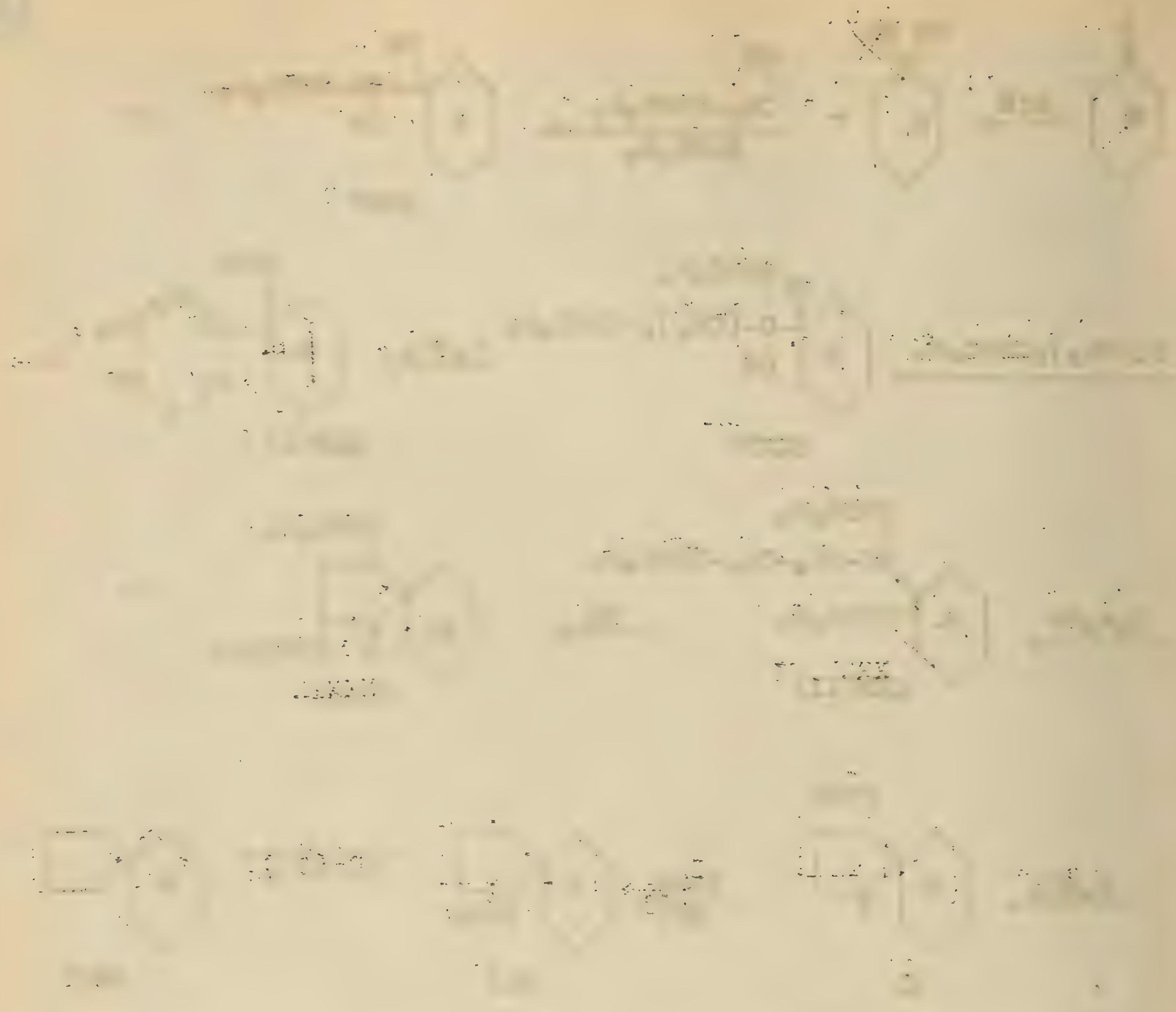


XXXV XXXVI XXXVII XXXVIII XXXIX XL XLI XLII

Replacing cyclohexanone in the above synthesis in turn by 4-methyl cyclohexanone, 3,3-dimethyl cyclohexanone, 2-methyl cyclopentanone, and cyclopentanone, he prepared four other spirans in low yield. The cyclopentanespirocyclopentane could not be dehydrogenated with selenium. The others were not tried.

An attempt was made to prepare cyclohexanespirocyclobutane by reacting XXXV with bromoethyl acetate instead of the chloropropionate. The synthesis went well through the tri-ester (homolog of XXXVIII), but the cyclization to the four-membered keto-ester (homolog of XXXIX) went in less than one per cent yield. It was not carried any further.

Sen-Gupta has offered a general explanation for the dehydrogenation of spiran hydrocarbons. Dehydrogenation cannot take place except by rupture of the spiran along the dotted line as shown. If this takes place, the intermediate may undergo a dual mode of cyclization to produce two different aromatic compounds. This explains all the examples given above, and makes the formation of mixtures on dehydrogenation seem logical.



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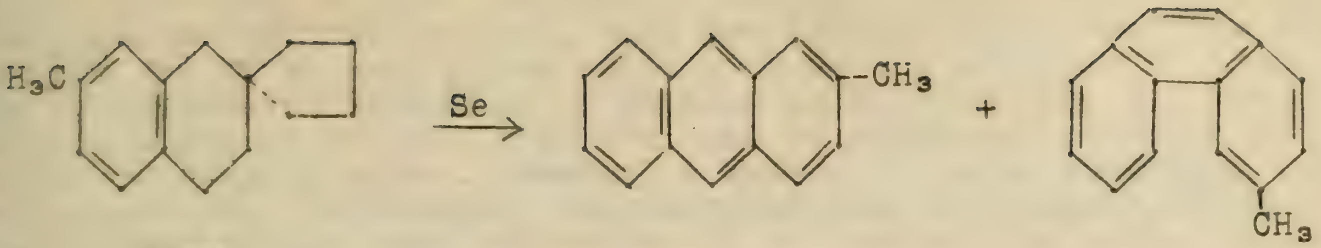

XLIII

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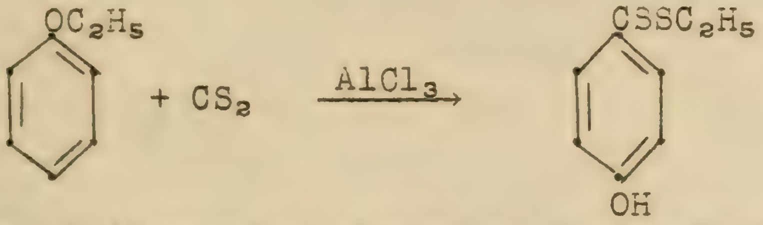
Reported by R. B. Wearn
May 14, 1941

UNUSUAL FRIEDEL CRAFTS REACTIONS

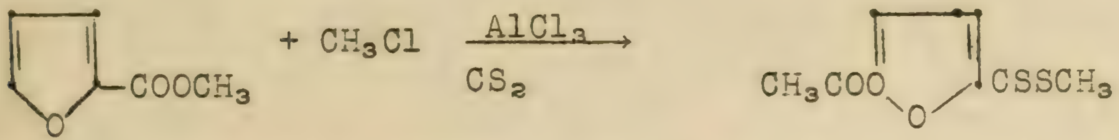
In 1877 Friedel and Crafts treated amyl chloride with aluminum and obtained a mixture of long chain hydrocarbons and alkyl halides. Since that time, a great variety of closely related reactions has been discovered. In general, they are condensation reactions involving the use of an activating agent such as the metallic halides. The Feidel-Crafts synthesis is usually associated with alkylation and acylation reactions involving the use of anhydrous aluminum chloride as the condensing agent. However, a number of other reactions such as rearrangements, reductions, dehydrogenations, and introduction of specialized groups into molecules may be carried out using modified Friedel-Crafts procedures.

Due to the wide diversity of the reaction and the exact knowledge as to its mechanism, it is difficult to differentiate between normal and abnormal reactions. From time to time, unexpected products have been obtained from Friedel-Crafts type reactions. Some of these are little known; yet are of interest.

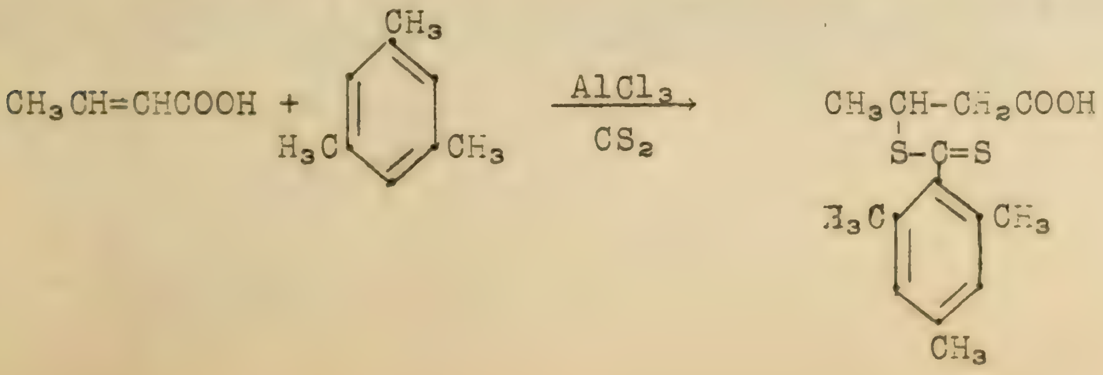
Although a number of different solvents can be employed for the reaction, carbon disulfide is the one most often used. It has been found, however, that under certain conditions the carbon disulfide molecule will enter the reaction in the presence of aluminum chloride. Jorg discovered this to be a fairly general case when the reacting molecules contained activating groups. For example, phenetole is readily converted to p-hydroxydithioethylbenzoate by means of aluminum chloride in carbon disulfide.



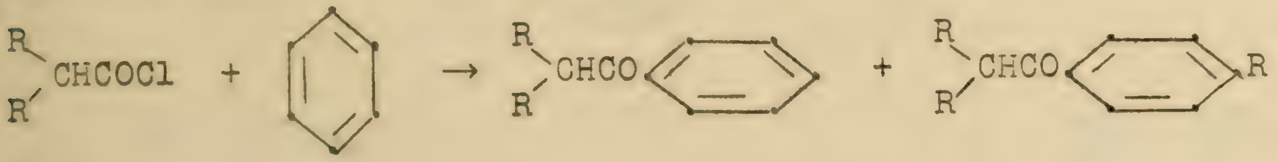
Gilman and Calloway have reported that methyl 2-furoate behaves similarly.



In this laboratory, a somewhat analogous reaction has been observed. An attempt to condense crotonic acid with mesitylene in the presence of carbon disulfide and aluminum chloride yielded an unexpected sulfur-containing compound. It is believed that the reaction proceeded in a manner like that of phenetole.

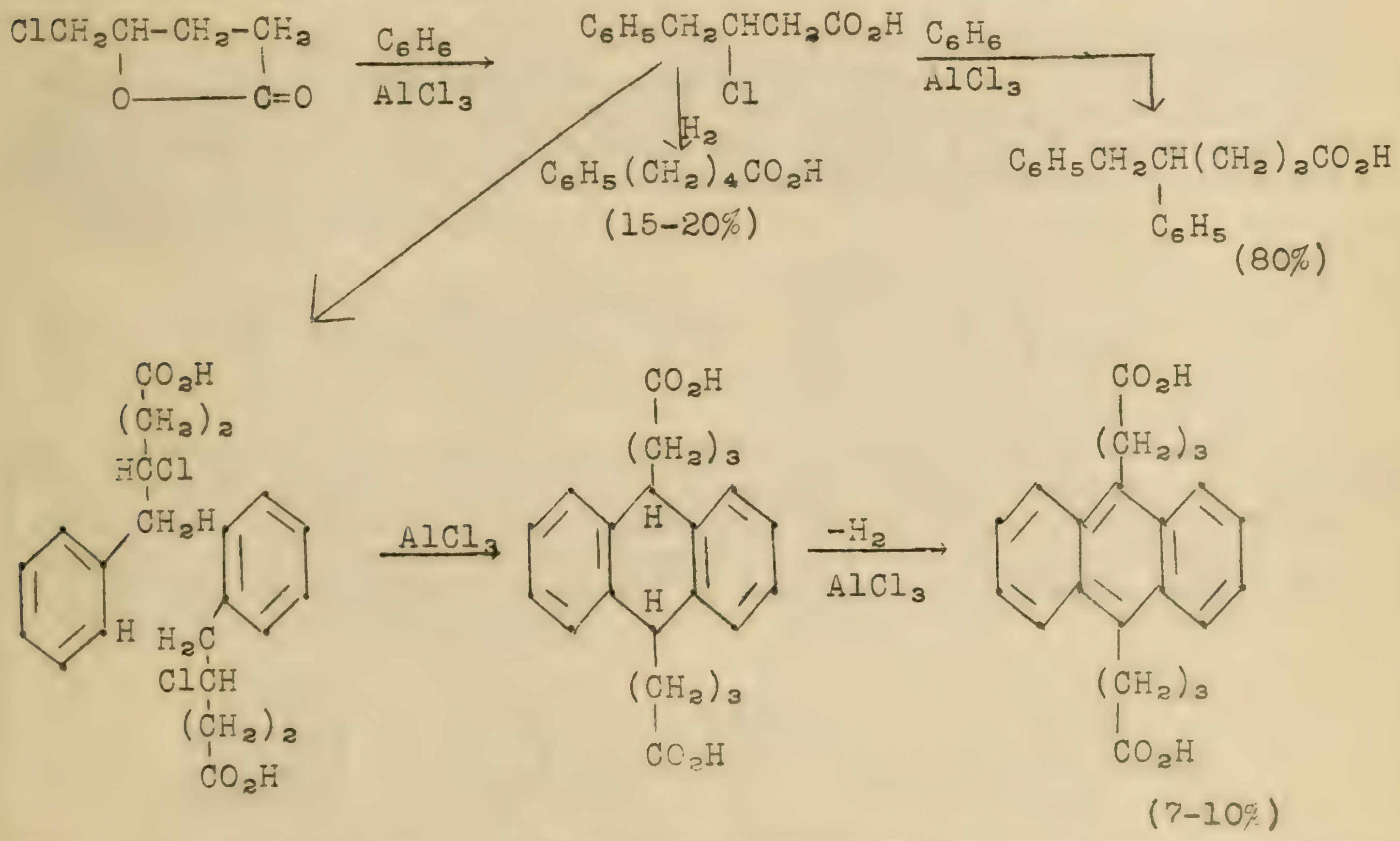


The wandering of alkyl groups in Friedel-Crafts alkylations has been known for some time. Recently Braun and Shattner have reported a new type of migration of an alkyl group. When the acid chlorides of dialkylacetic acids were condensed with benzene, a fair yield of a nuclear substituted dialkylacetophenone, beside the expected dialkylacetophenone, was obtained.

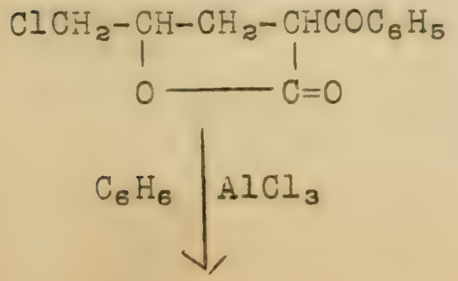


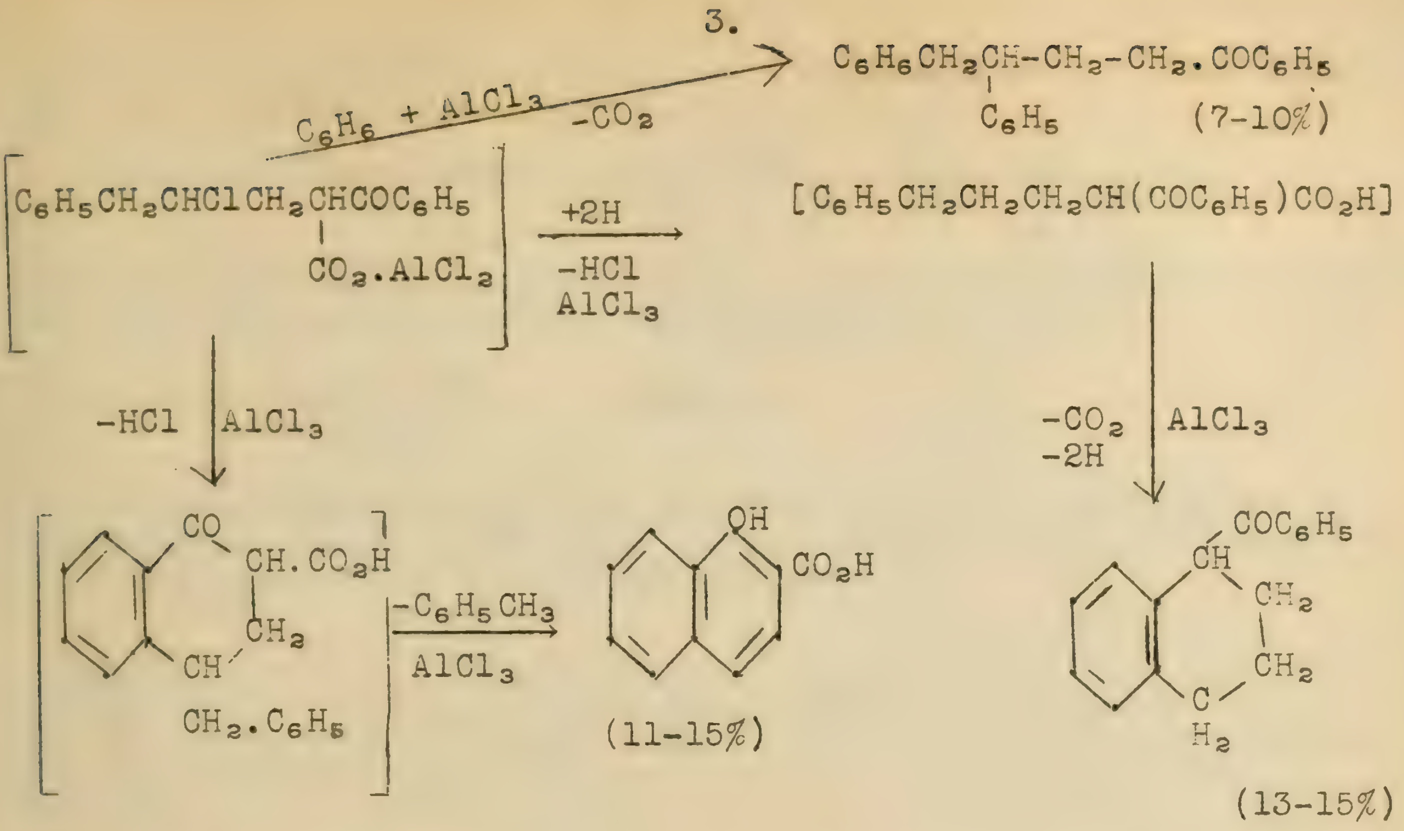
The alkyl group always occupied the position para to the carbonyl group. It was observed that the reaction did not take place if the R groups were methyl or if acid chlorides of higher dialkylated acids were employed.

Beyer and coworkers have obtained some unusual results by treating halogenated lactones with aromatic hydrocarbons in the presence of aluminum chloride. For instance, 5-chloro-   -valerolactone is believed to undergo the following transformations.

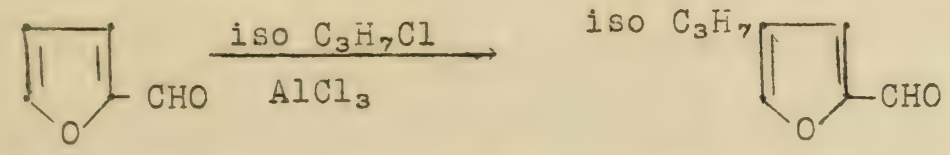


When α-benzoyl-δ-chloro-γ-valerolactone was reacted under similar conditions a variety of products was obtained.

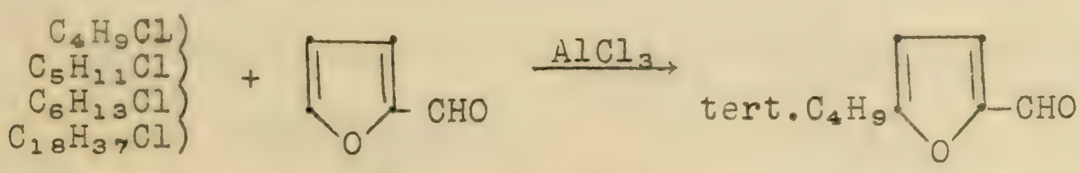




In general, attempts to alkylate unsubstituted heterocyclic rings have been unsuccessful. However, numerous examples of alkylation of substituted heterocyclic compounds are known. A monosubstituted furan usually substitutes in the 2 or 5 positions. The reaction of furfural with isopropyl chloride gives the unexpected 4 substituted derivative.



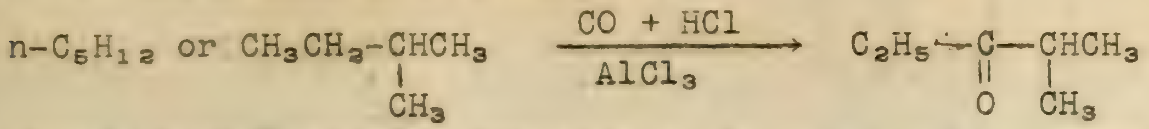
If the higher homologous halides like branched butyl or amyl chlorides are used to alkylate furfural, the group enters position 5. Furthermore, with certain furamic compounds, in addition to the isopropyl residue, no group except the tert.- butyl has been introduced regardless of whether the starting reagents were butyl, amyl, hexyl, or even n-octadecyl halides.



The Friedel-Crafts reaction is generally associated with aromatic chemistry although numerous examples of its application to aliphatic chemistry are known. The higher members of the paraffin series can be acylated to give a mixture of saturated and unsaturated ketones.

$$n\text{-}C_5H_{12} \xrightarrow[AlCl_3]{CH_3COCl} 2\text{-}(CH_3CO)C_5H_{11}$$

Anomalous results were obtained when an attempt was made to carry out the Gattermann-Koch synthesis.

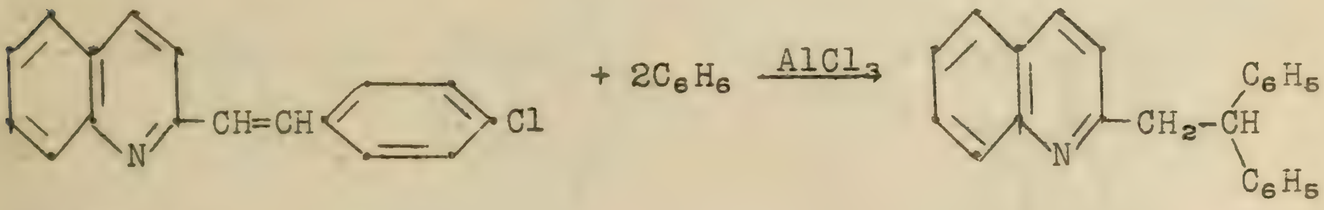


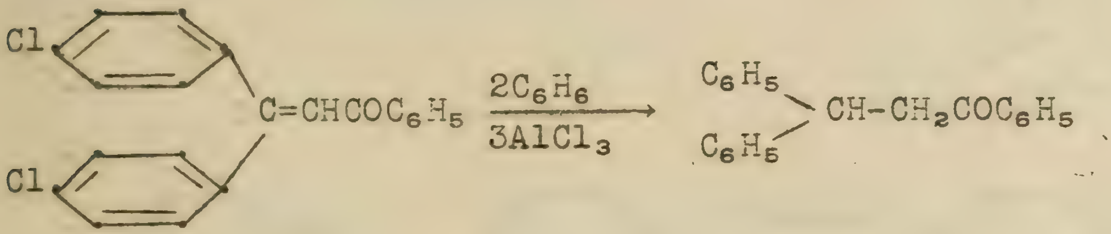
$$n\text{-}C_5H_{12} \text{ or } CH_3CH_2\text{-}\underset{\displaystyle CH_3}{\underset{|}{CHCH_3}} \xrightarrow[AlCl_3]{CO + HCl} C_2H_5\text{-}\underset{\displaystyle O}{\underset{\|}{C}}\text{-}\underset{\displaystyle CH_3}{\underset{|}{CHCH_3}}$$

Another interesting observation was made on the treatment of alkyl halides with carbon monoxide and aluminum chloride.

$$n\text{-}C_3H_7Cl \xrightarrow[AlCl_3]{CO + HCl} n\text{-}C_3H_7COCl$$

It has been demonstrated that the Friedel-Crafts reaction is an equilibrium reaction and under certain conditions is reversible. This has been proven in several instances.





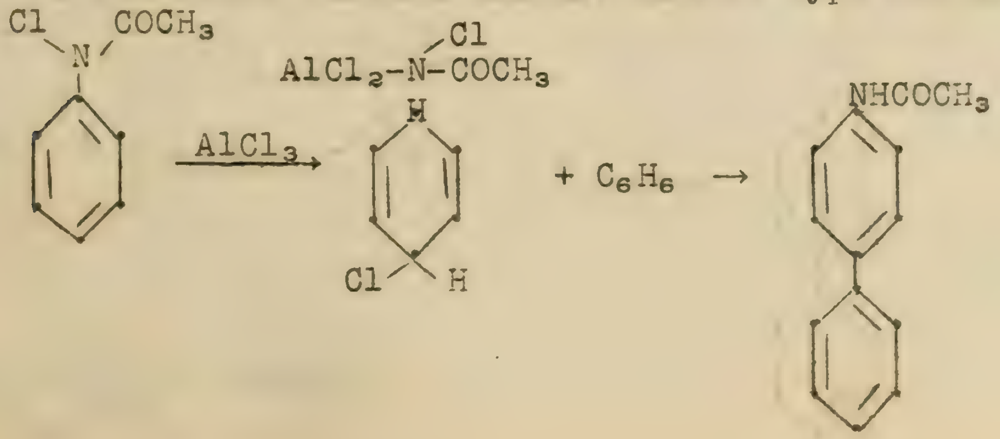
Of the less commonly used condensing agents for the Friedel-Crafts synthesis, one might mention phosphorus pentoxide, mercuric chloride, and the aliphatic chloro-acids or chloro-anhydrides. An interesting example of the use of the latter is in the preparation of p-methoxyacetophenone.

$$CH_3OC_6H_5 + (CH_3CO)_2O \xrightarrow{ClCH_2CO_2H} p\text{-}CH_3OC_6H_4\ COCH_3$$

Prolonged refluxing of the reagents produced a yield of 80-90 per cent whereas without the chloroacetic acid a yield of only 1.5 per cent was obtained.

A few other unusual Friedel-Crafts type reactions are;

1.



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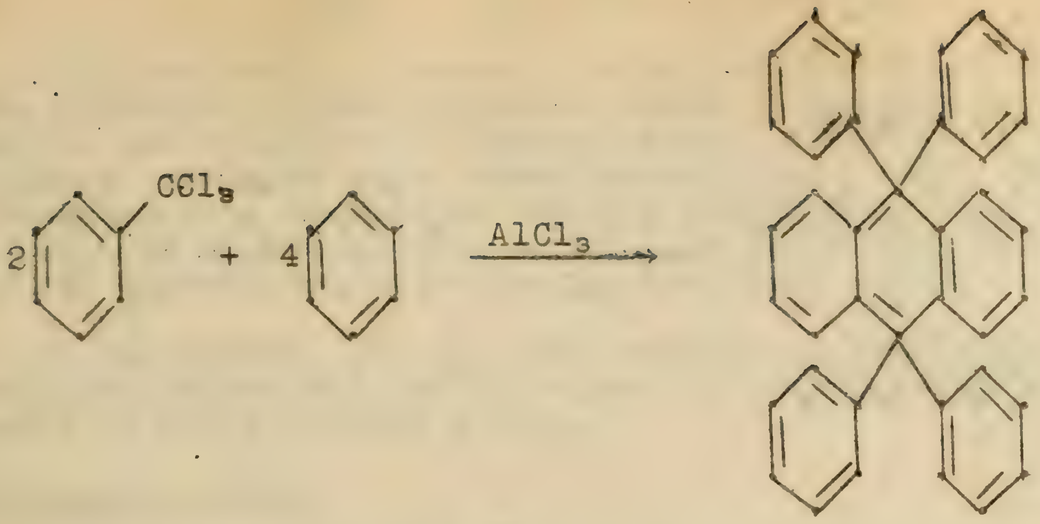

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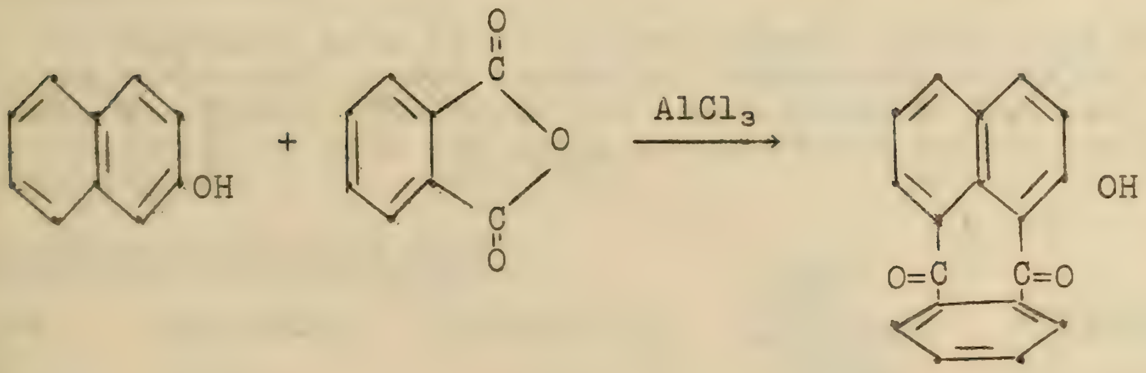

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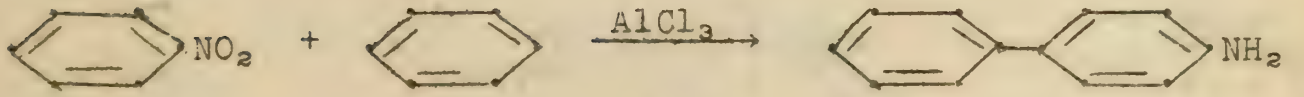

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v. Braun and Schattner, ibid., 74, 22 (1941).
Jorg, ibid., 60, 1466 (1927).
Gilman and Calloway, J. Am. Shcm. Soc., 55, 4197 (1933).

Reported by N. Rabjohn
May 21, 1941

A STUDY OF 3-AROYLACRYLIC ACIDS

Lutz - University of Virginia

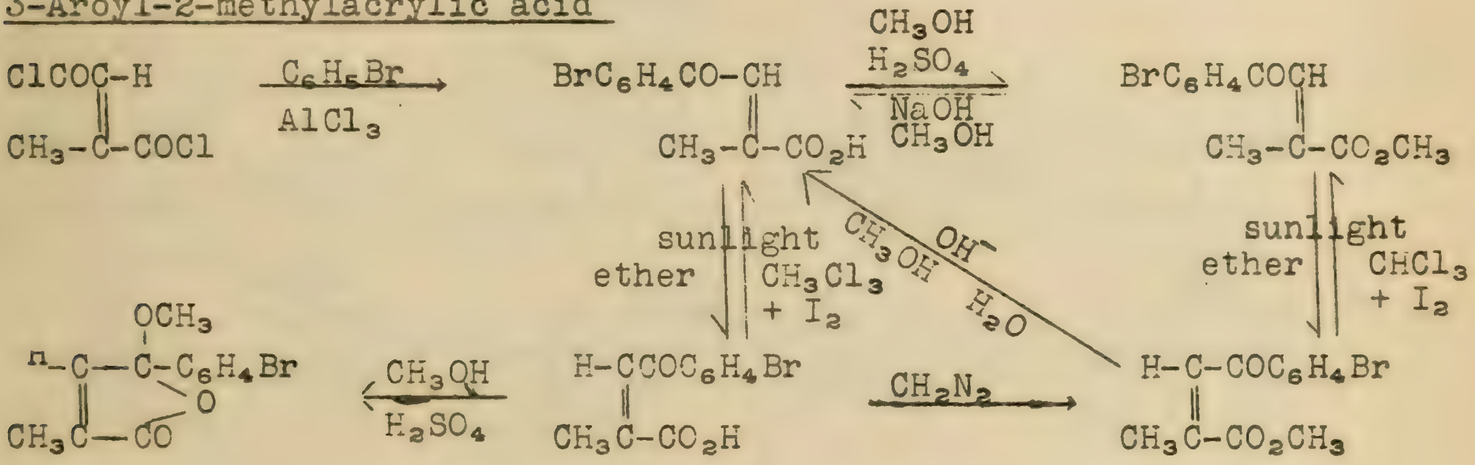
Lutz has made a systematic study of the effect of substitution on the stability of the geometric forms of β-aroylacrylic acids. The formation and reactions of lactonols and lactamols in the cis acids and amides have also been investigated. Lutz found that a methyl on the 3-carbon atom stabilized the cis form better than a methyl on the 2-carbon atom of the acrylic acids. He found that methyls on both the 2 and 3 positions made the cis form very stable.

In the amides, the cis form existed in the lactamol form except in the cases where all the hydrogens on the nitrogen have been replaced by alkyl or aryl groups.

3-Aroylacrylic acid

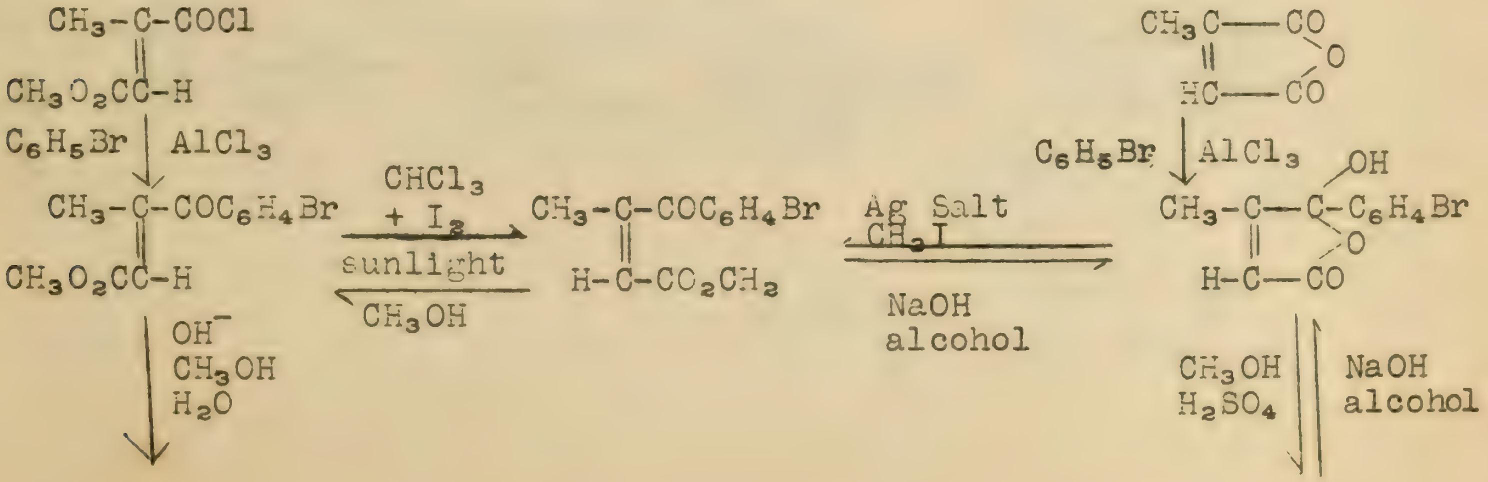
The compounds made by the Friedel-Craft reaction of benzene on maleic anhydride and on the monomethyl ester-acid chloride of fumaric acid were identical. Inversion had taken place in the case of the maleic anhydride to give the trans acrylic acid indicating it to be the stable form.

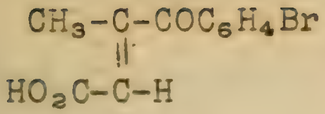
3-Aroyl-2-methylacrylic acid



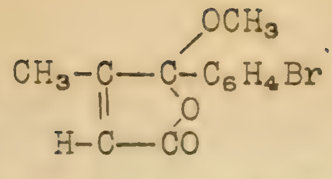
Both the cis- and trans-acids are reduced by zinc in acetic acid to $BrC_6H_4COCH_2CH(CH_3)CO_2H$. The trans-acid is split by $Ba(OH)_2$ to p-bromoacetophenone proving the position of the methyl group.

3-(p-Bromobenzoyl)-3-methylacrylic acid

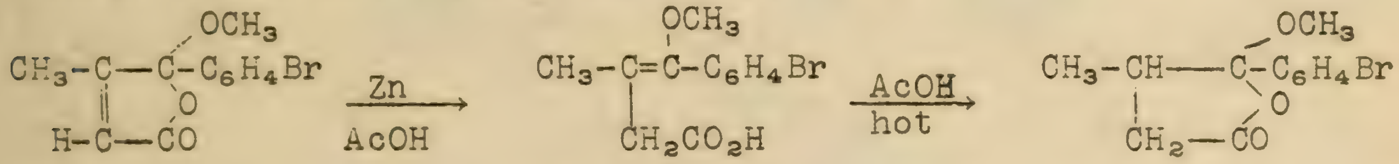




$$\begin{array}{l} CH_3-C-COC_6H_4Br \\ \qquad \| \\ HO_2C-C-H \end{array}$$

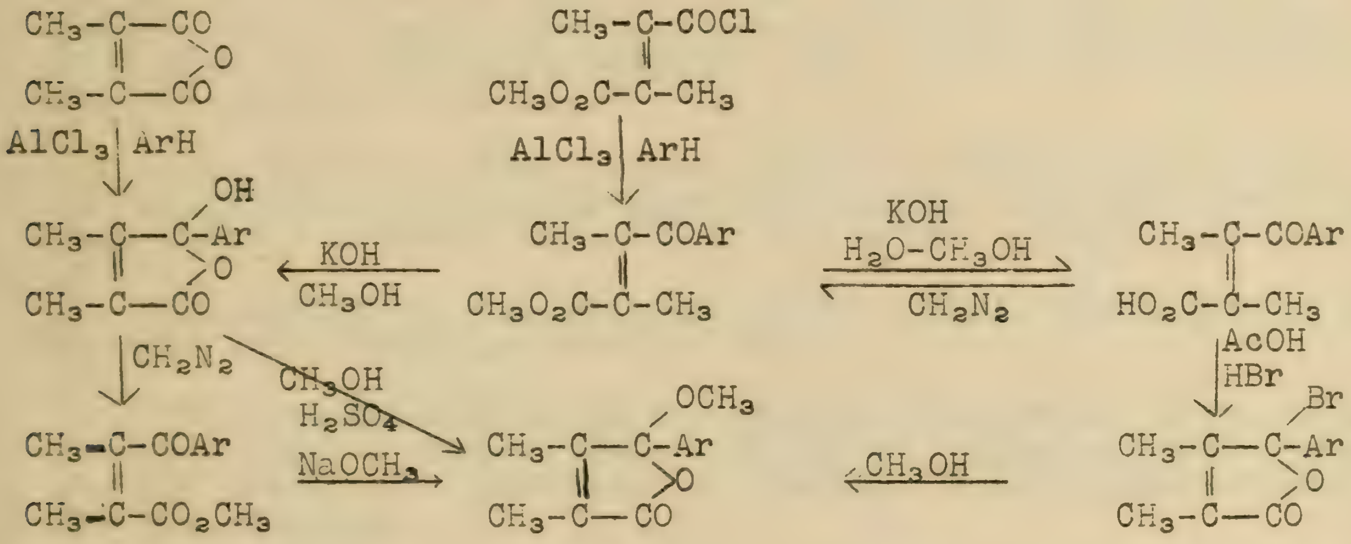


The trans-acid is reduced by zinc and acetic acid and the cis-acid by sodium hydrosulfite to $BrC_6H_4COCH(CH_3)CH_2CO_2H$. The cis-acid gives p-bromopropiophenone on hydrolysis with $Ba(OH)_2$. Zinc and glacial acetic acid reduce the cis-acid in another manner.

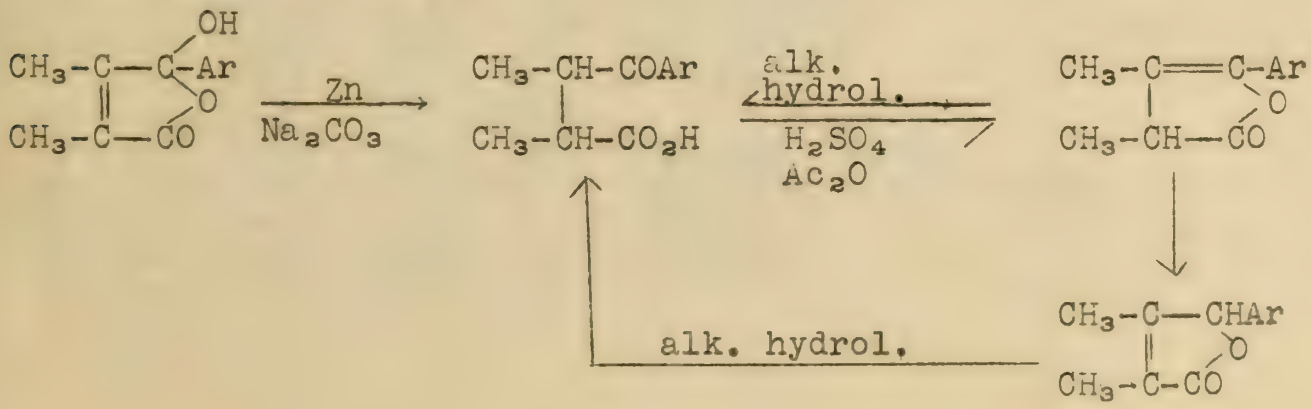


This cyclic ester is easily rearranged with methanol-sulfuric acid to the normal ester.

3-Aroyl-2,3-dimethylacrylic acid

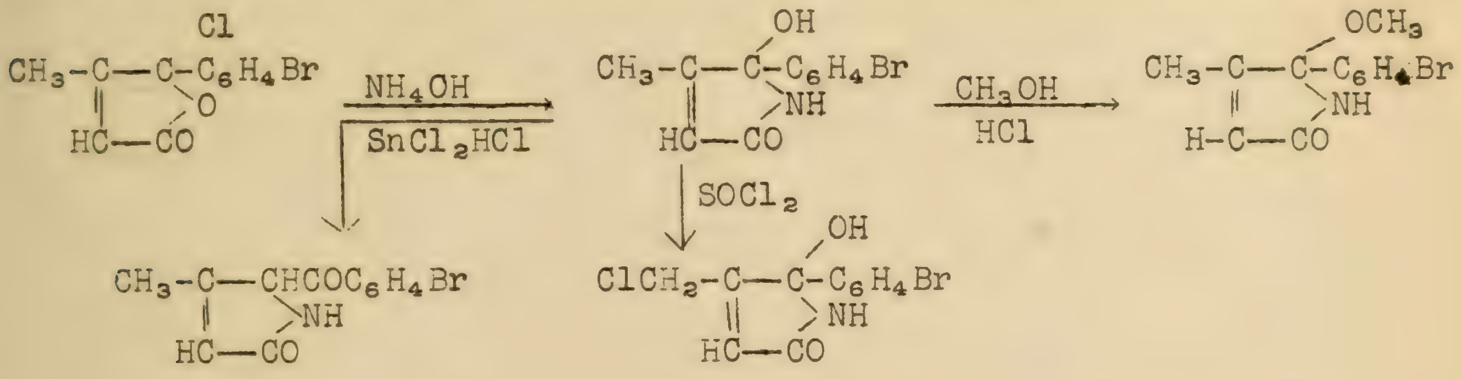


Reduction of both the cis- and trans-normal esters with zinc and acetic acid gave mixtures of the stereoisomeric forms of $ArCO-CH(CH_3)CH(CH_3)-CO_2CH_3$. The cis-acid was not reduced by zinc and acetic acid although the trans-acid was. However, the cis-acid could be reduced with zinc and sodium carbonate to the same acid. This acid is easily isomerized.



3-(*p*-Bromobenzoyl)-3-methylacrylamides

The object of this investigation was to study the ring-chain tautomerism and the possibility of isomerism in the *cis*-compounds. The pseudo acid chloride, the pseudo ester and the normal ester of the *cis* form all give the lactamol when treated with ammonium hydroxide.



The action of thionyl chloride on the hydroxypyrrolinone structure brought about chlorination in the methyl group. The structure was still that of a hydroxypyrrolinone since its reactions paralleled that of the parent amide.

The amides obtained by the action of methyl amine on the pseudo acid chloride of the cyclic *cis*- acid has the lactamol structure. Again thionyl chloride chlorinated the methyl group in the side chain.

The action of dimethylamine on the pseudo acid chloride gives the true open chain *cis*-dimethyl amide.

The N-methylanilide of the *cis* acid also proved to be an open chain compound if made by inversion of the *trans*-anilide. If made from the pseudo acid chloride the isomeric N-methylanilinofuranone form was obtained.

The *trans*-anilide on inversion gave the hydroxypyrrolinone structure. The pseudo acid chloride reacted with aniline to give the anilinofuranone. The true open chain *cis*-anilide is incapable of existence.

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